THE LANCET

FOUNDED BY THOMAS WAKLEY IN 1823

VOLUME TWO
JULY–DECEMBER
1958

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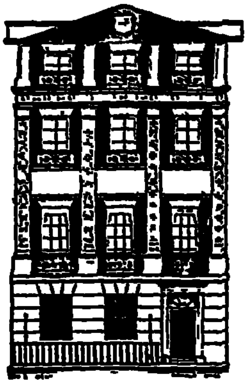

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PUBLISHED by the PROPRIETORS, THE LANCET LIMITED 7, Adam Street, Adelphi, in the County of London
Printed by HAZELL, WATSON AND VINEY LTD, Slough and Aylesbury—Saturday, March 21, 1959
PRINTED IN GREAT BRITAIN—Entered as Second Class at the New York, U S A, Office

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are 11 6 beds per 1000, but only some 80 admissions per 1000 per year The only fully documented and detailed studies of bed requirements in this country, those of the Nuffield Trust, suggest that we have more beds than we need for our present turnover Certainly we need nothing like the 14 beds per 1000 that were suggested in the memorandum on development of consultant services, or the 8 or so non-mental beds per 1000 suggested in some of the hospital surveys of 1943–44

Modern development is toward putting the acute psychiatric unit and the acute geriatric unit in the general hospital, and beds provided for one purpose should be so arranged that they can be equally well used for another, most of our current new planning at a rate of some 3 beds per 1000 has a reasonable margin. It is vital, however, to avoid cramping the outpatient and diagnostic departments and operating-theatres These are the real key departments, beds are secondary to them and can be far more easily and economically increased if they are really proved necessary by experience Whatever new hospital development is planned there should be space for addition

Development is, therefore, likely to be on the lines of replacement of multiple, small, bad, old hospitals by larger, well-planned, modern hospital units in smaller numbers and in many areas with fewer beds in all. We then face the problem of how far this process of concentration should be carried There are various limiting factors in this It is commonly accepted in Britain that hospitals should not be too large The service in a city of the size of Sheffield, for instance, serving 600,000–700,000 persons, should not be concentrated in one central group of buildings British thinking is against what amounts to a hospital town, a unit so large as to be cut off from the community of which it is or should be a part and drawing patients too far from their own localities So far as the big cities are concerned, opinion in England favours the main area general hospital of the order of at most 600 beds, perhaps with associated special facilities including an acute psychiatric unit and facilities for the care of the chronic sick, and sometimes a small number of detached units—for instance, a long-stay annexe or a maternity unit. Such a hospital is large enough to provide adequate specialist units in all the ordinary specialties It is easy to devise a pattern for one of our cities, say, Liverpool with a central teaching hospital of larger size and an inner and outer ring of general hospitals, each of 600 beds or so, disposed at suitable points of confluence of public transport for the convenience of the public. Obviously this sort of pattern will not be reached for many years because it involves replacement of most of the existing hospitals It must be flexible because succeeding generations will certainly want to vary it, in detail if not in essentials, but any new building now could be arranged to fit in with such a plan without throwing away effort on patching or extending unsuitable old hospitals

Outside the big cities the needs of substantial county towns are relatively clear A single general hospital, perhaps with some detached annexes for long-stay cases, can provide ultimately all the hospital service that is needed The mistake that can be made is that long-term planning can be distorted by a mistaken desire to conserve unsatisfactory pieces of old hospitals which will never fit efficiently into a new unit; or, worse still, several separate hospitals, each too small, may be preserved

Elsewhere much more difficult considerations arise. Broadly, public transport determines the foci at which hospitals should be developed People should be able to get to their hospitals as they are able to get to towns for other purposes The special problems arise where, as in West Cornwall, there is a multiplicity of small towns each with its own small hospital. In such places ultimately the small units must give way to a central general hospital which will be an adequate base for the development of specialist services The right place is largely determined by the integration of bus and rail services The most satisfactory population grouping is of the order of 100,000 upward, with an upper limit around a quarter of a million Local considerations of transport, site location, and past practice must come into these decisions, for a uniform pattern supposedly ideal would inevitably be stultifying

There are some population groups which are so detached as to make necessary hospital provision on a smaller scale than would normally be considered. Places like Berwick and Aberystwyth are very far from any main centre and serve populations too small to support the general hospital of 250 beds or so which would normally be regarded as a minimum Geography makes it necessary to have such detached units, but they should be at least large enough to provide work for locally resident physician, surgeon, and obstetrician and visiting specialists in other fields The general hospital with no locally resident specialist staff is an anachronism

We must guard against the vanity of too firm, remote planning, until there is some experience with modern area hospitals There is insufficient basic information, and however clear may be theoretical concepts developed at the centre they must often be modified in the light of local knowledge and feeling The problem is to avoid a sentimental dispersal of effort which would too greatly reduce the effectiveness of the hospitals we provide No attempt has been made to discuss the general-practitioner cottage hospital because, although we have many such, their use varies greatly and no clear pattern for their future can be discerned There are too many serious lacunæ in the provision for specialties to contemplate much new development otherwise, except in giving general practitioners access to beds especially for maternity cases

Infectious disease is a declining problem both in and out of hospital Separate hospitals for these diseases can have no place in future planning unless it be in the largest cities, and even there I doubt whether they will survive long Tuberculosis is by no means conquered yet, but the mortality has fallen by two-thirds and morbidity by more than a quarter, already many beds for tuberculosis are redundant and more become so yearly The day of the separate sanatorium is probably short, and treatment of tuberculosis within the foreseeable future will probably be undertaken largely in special wards of general hospitals In turn, there will be a reduction in the demand for thoracic surgical facilities for tuberculosis while there has arisen a new problem in cancer of the lung, which is certain to grow for some years to come. Yet this disease presents a smaller problem than tuberculosis in the demand it will make upon hospital beds, for it is either extirpated by surgery or it is much more rapidly progressive than tuberculosis Cardiac surgery has increased rapidly and will remain with us, but probably not to produce any great further increase in the load. Special units for neurosurgery and plastic surgery probably need material further increase, but they in turn will reduce the load on general and traumatic surgery. Pædiatric departments grew rapidly in the early years of the service, but that growth has passed its peak five years ago and it is doubtful whether we will continue to need so many beds as we have now, in areas such as London, Manchester, and Liverpool a pronounced decline has occurred and the total pædiatric admissions, starting at 91,205 in 1949, rose to a maximum of 121,208 in 1952 and fell to just over 100,000 in 1956 Other special departments, such as genito-urinary surgery, will probably grow, but if they do it will be at the expense of general surgical facilities which they replace in part

Early ambulation after surgery and shorter stay will reduce the number of surgical beds required for the same number of patients, but the surgical waiting-lists are so long and are falling so slowly that more facilities are needed Even with more operating-theatres and appreciably faster turnover, it may well be that the present requirement will remain and some territorial redistribution will certainly be needed On the other hand, medical beds are far less heavily pressed, although in some areas they are manifestly too few Between these two main specialties much geater flexibility is needed, freeing beds for medical cases in the first three months of the year, when respiratory illness is at its height, and returning them for surgical work in later months of the year

Probably the most striking changes will occur in the use of beds for the mentally ill In the past five years there has been a rapid increase in the provision of treatment for the mentally ill outside hospital, and the probable development of the future is in psychiatric units at general hospitals rather than in large numbers of beds in detached mental hospitals New psychiatric outpatients, other than those seen for mental deficiency, doubled in number between 1954 and 1956, probably because of an increase not so much in illness as in readiness to accept early treatment The separate mental hospital will be with us for many years yet, but it is likely that new provision will be mainly at general hospitals with inpatient, day-hospital, and outpatient facilities Experience in some of the psychiatric units of general hospitals in the Manchester region and elsewhere suggests that, in this way, a much smaller number of beds can provide for a given population than has been thought necessary in the past

Much of this comment on the hospital service is by way of forecasting trends The precedents show that most forecasters have been wide of the mark I pretend to do no more than mark some trends already discernible which seem to me most likely to survive There remains the major issue I said at the beginning that the health service was primarily one of home care If that is so, the hospitals must be organised primarily for the support of home care They are consultative centres for special diagnosis and treatment, but they must be more than that They are not the centres of general practice, but they must be accessible to the general practitioner In some hospitals there is already clearly realisation of the necessity of closer liaison between special and general medical practice As specialism becomes more complicated and more abstruse, this association becomes more than ever necessary The family doctor is the only person who sees the patient whole in relation to his family and his job, as well as to his illness It is necessary, therefore, that the family doctor should not merely have diagnostic aids from the hospital but also be enabled to make his own peculiar contribution to the assessment and care of the patient who goes to hospital, both when he is there and when he has returned home The sojourn in hospital is a brief incident in the patient's life, in a foreign environment, it may have a continuing effect It is important that that effect should be as favourable as medicine as a whole can devise, but that is only practicable if there is close partnership between those inside and those outside hospital, whatever their profession

PHARMACOLOGY AND CLINICAL USE OF PEMPIDINE IN THE TREATMENT OF HYPERTENSION

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BEFORE the introduction of mecamylamine, all effe ganglion-blocking drugs used in the therapy of h tension were quaternary ammonium derivatives T drugs are not freely diffusible across cell membr including those of the gastrointestinal tract (Paton Zaimis 1952) Since their absorption from the gut is incomplete, and unpredictable, oral therapy is difficu control and often ineffective In contrast, mecamyla is a secondary amine which is freely and rapidly abso from the gut (Milne et al 1957), and is therefore al given by mouth

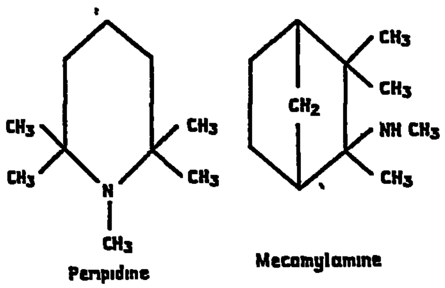
Although mecamylamine has become very popula the treatment of hypertension, it has several disadvant

Since its excretion is slow and irregular (Allanby Trounce 1957, Milne et al 1957) toxic effects from overd may be prolonged for several days, sometimes with dang life *Of these effects, paralytic ileus is the most impor* Resultant vomiting and diarrhœa cause reduction of blood-flow with further delay in excretion of the drug prolongation of toxic effects Patients with mecamylamine have been diagnosed by unsuspecting surgeons as case acute intestinal obstruction, and exposed to the dange unnecessary laparotomy (Grant and Boyd 1957, pers observation 1958) Mecamylamine diffuses freely into central nervous system, and accumulation within the brain lead to tremors and incoordination (Schneckloth et al 1 Harington and Kincaid-Smith 1958)

In view of these disadvantages, we were glad to st another drug of the amine, ganglion-blocking t preliminary laboratory findings of which were submit to us in October, 1957, by Messrs May & Baker L For this new drug (1 2 2 6 6-pentamethylpip dine) originally designated M & B 4486, the common na pempidine ('Perolysen', May & Baker) has been p posed While closely resembling mecamylamine, it important differences in detail which may make it a m useful antihypertensive agent It will be necess throughout to compare the pharmacology of these sup ficially similar drugs Supplies of pempidine were m available to us on Jan 1, 1958, together with detai pharmacological, biological, and toxicological data (S Corne and N D Edge, *personal communication*), n published in summary form (Lee et al 1958) An in pendent report on the basic pharmacology of pempid and other piperidine derivatives has also been publish recently (Spinks and Young 1958)

Chemistry

Pempidine, a tertiary amine, is a simple derivative of pipe dine of empirical formula $C_{10}H_{21}N$, and molecular weight 15 Fig 1 shows the structural formulæ of pempidine and me mylamine Both compounds are relatively strong bases of p about 11 0, and are therefore administered as salts Pempid is available for oral use as the bitartrate, but the hydrochlor



1—Structural formulæ of pempidine and mecamylamine In oth instances the amine radicle is surrounded by numerous nethyl groups

preferred for the intravenous route Since the drug is freely sorbed from the gut, the parenteral preparation is chiefly research interest and will have little place in practical therautics The hydrochloride contains about 80% of active mpidine base, and the bitartrate about 50% The drug has armacological and chemical properties quite distinct from ose of the much more toxic unsubstituted amines, piperidine d N-methylpiperidine This is of theoretical interest in lation to the mode of action of the amine ganglion-blocking oup of drugs Other piperidine derivatives have previously en shown to have ganglion-blocking activity (Norton and hillips 1953), but pempidine is the first to be suitable for use human therapeutics

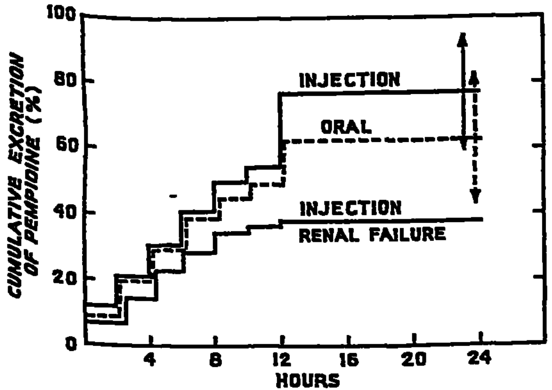
Pharmacology

The experimental design was similar to that used in an vestigation of mecamylamine (Milne et al 1957) The sults obtained in the two series of observations can thus e directly compared

bservations in Man

32 hypertensive patients without renal failure were ven pempidine, and of these 27 received continuous eatment In addition, observations were made in 2 cases f hypertension complicated by moderate uræmia (bloodrea approximately 100 mg per 100 ml)

Observations were made of the excretion of a single 5 mg ose of pempidine hydrochloride given by intravenous injection t 9 A.M Since it is known that the excretion of mecamylamine considerably influenced by variation of urinary pH (Baer et l. 1956, Milne et al 1957), the separate effects of simultaneous dministration of ammonium chloride, sodium bicarbonate, r acetazolamide on the excretion and pharmacological action f pempidine were studied in detail Ammonium chloride, g four times daily or sodium bicarbonate 3 g four times aily, was given by mouth on the day preceding and the day of injection of pempidine During trials with acetazolamide, 250 mg was given orally at the same time as the pempidine injection and a further 250 mg six hours later Urine was collected at two-hourly intervals for twelve hours after administration of pempidine, and a further twelve-hour sample from 9 P.M to 9 A.M was collected to complete a twenty-four-hour period In the cases of renal failure, additional twenty-four-hour samples were obtained on the second and third days after the injection Each first-day collection period therefore involved analysis of 8 urine samples, 7 after the injection and 1 pre-injection blank sample 32 collection periods have been analysed, comprising 8 from patients after pempidine alone, 8 from patients receiving additional ammonium chloride, 8 from patients receiving either sodium bicarbonate or acetazolamide, 2 from cases of moderate renal failure, and 6 from patients receiving a single oral dose of pempidine, ranging from 5 to 15 mg of the bitartrate



ig 2—Mean cumulative excretion of pempidine during the first 24 hours after an intravenous injection or an oral dose of the drug in hypertensive patients without renal failure, and after an intravenous injection in patients with renal failure The standard deviations of the 24-hour excretion levels are shown by the vertical lines

A total of 90 daily collections of urine from 10 hypertensive patients on continuous routine treatment with pempidine bitartrate were analysed The effects of ammonium chloride, 2 g q i d for three days, and sodium bicarbonate 3 g q i d for three days, on excretion and antihypertensive action were examined

Distribution of the drug in human blood in vivo could not be determined, because the analytical methods were too insensitive Distribution of pempidine in vitro was determined after addition of pure pempidine hydrochloride to blood sufficient to give an average concentration of 25 µg per ml Plasma-protein binding was determined after pressure filtration through 'Cellophane', and entry of the drug into erythrocytes after centrifuging Entry of pempidine into leucocytes was investigated in a sample of blood from a case of chronic lymphatic leukæmia with a white-cell count of about 300,000 per c.mm

TABLE I—STATISTICAL ANALYSIS OF EXCRETION OF PEMPIDINE IN MAN, AND COMPARISON WITH THE EXCRETION OF MECAMYLAMINE

Comparison	Mean I	Mean II	t value	P
Excretion of injected dose (I) v excretion of oral dose (II)	76%	63%	1·2	0·3>P>0·2
Excretion in acid urine (I) v excretion in alkaline urine (II)	78%	55%	2·2	<0·05
Excretion pempidine in acid urine (I) v excretion mecamylamine in acid urine (II)	78%	56%	2·9	<0·02
Excretion pempidine in normal urine (I) v excretion mecamylamine in normal urine (II)	76%	37%	6·7	<0·001
Excretion pempidine in alkaline urine (I) v excretion mecamylamine in alkaline urine (II)	55%	13%	6·0	<0·001

Observations in Rats

These experiments were designed to investigate the distribution of the drug in various body tissues 2 rats were given sublethal intraperitoneal injections of 16 mg per kg body-weight of pempidine base and a further 2 rats lethal intraperitoneal injections of 175 mg per kg Samples of blood and various tissues were analysed after one hour in the former and immediately before death in the latter Rats die in respiratory paralysis twenty to twenty-five minutes after lethal injection of the drug

Chemical Methods

Pempidine was estimated by combination with methyl-orange as first described by Brodie and Udenfriend (1945) and modified by Tillson et al (1954) A full discussion of this accurate but non-specific method has been given previously (Milne et al 1957) Tests for specificity in the particular experimental conditions were made by paper chromatography after extraction of urine samples by dichlorethane The chromatogram was developed either by butanol-acetic acid or phenol-water, and the position of the pempidine spot demonstrated by the method of Chargaff et al (1948) The only spot from urine samples which gave a methyl-orange reaction after elution had an R_f value identical with pure pempidine (R_f in butanol-acetic

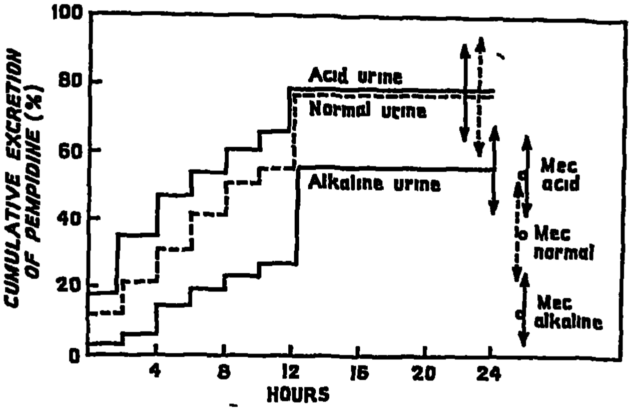


Fig 3—Mean cumulative excretion of pempidine during the first 24 hours after a single intravenous injection of 5 mg of the hydrochloride in hypertensive patients without renal failure Excretion rates are decreased in patients with alkaline urine and slightly increased in patients with highly acid urine The vertical lines give the standard deviation in each case Cumulative excretion of mecamylamine in 24 hours is shown for comparison The lowest rate of excretion of pempidine in alkaline urine is similar to the highest rate of excretion of mecamylamine in acid urine

acid 0 72) This proves that pempidine is probably excreted unchanged but does not absolutely exclude the possibility of partial metabolism to another amine of identical chromatographic properties Pure specimens of pempidine can be recovered from urine of patients treated with the drug by addition of sodium hydroxide and subsequent extraction with dichlorethane

Results

Fig 2 compares the cumulative excretion of pempidine after intravenous or oral administration in hypertensive patients, and the excretion after intravenous injection in 2 cases of renal failure An average of 76% of an injected dose and 63% of an oral dose was excreted in the first twenty-four hours This difference is not statistically significant (table I) In the uræmic patients the mean cumulative excretion was 37% of the dose in the first day, and 62% in the first two days These results suggest that pempidine is completely absorbed from the gut, and that its elimination is delayed if there is renal failure

Fig 3 compares the cumulative excretion of pempidine in patients without prior preparation, and patients receiving ammonium chloride, sodium bicarbonate, or acetazolamide The latter two agents had identical effects in reducing excretion and therefore the results have been taken together

Excretion of pempidine is considerably reduced by alkalinisation of the urine ($P<0.05$; table I) Acidification of the urine increases excretion in the first few hours after injection of pempidine, but the total cumulative excretion in twenty-four hours is not significantly changed Cumulative excretion of mecamylamine under identical conditions is included in fig 3 for purposes of comparison Pempidine excretion is about twice as rapid as that of mecamylamine in patients with urine of normal pH, four times as rapid if the urine is alkaline, and one and a half times if the urine is acid Table I shows that these differences are all statistically significant

The average recovery of pempidine from twenty-four-hour urine specimens obtained from patients on continuous therapy was 95% of the ingested dose (S D 28%) The effect of varying the pH of the urine was studied in 6 patients only Ammonium chloride had little effect in 5 patients on the excretion of pempidine or on the clinical effects of the drug In 1 patient excretion was approximately doubled on the first day of ammonium chloride, accompanied by a slight rise of blood-pressure Sodium bicarbonate had a more obvious effect Excretion of pempidine was reduced in 4 out of the 6 patients, with a parallel increase in therapeutic and side-effects due to the drug minimum twenty-four-hour recovery of pempidine in four patients during sodium bicarbonate treatment was 23 39%, 52%, and 59% respectively An example of the of alkalinisation of the urine in 1 of these patients is in fig 4

These results suggest that the drug is almost excreted in the urine Acidification and alkalinisatio the urine during maintenance treatment had less effe the case of pempidine than in that of m (Milne et al 1957)

Distribution in Blood

Plasma levels during therapy were consistently low, less than 0 5 μg per ml At these levels the analytical too insensitive to give accurate results The drug is not ficantly bound to plasma-protein, concentrations in filtrates of plasma being slightly higher than those of plasma itself In contrast, 25% of mecamylamine is boun plasma-protein Pempidine readily diffuses into eryth the mean erythrocyte/plasma ratio in human blood being *Like mecamylamine, pempidine is concentrated within* cytes, the leucocyte/plasma concentration ratio in the of leukæmic blood being 12 *0*

Distribution in Tissues

Mean concentrations of pempidine in various rat after sublethal and lethal intraperitoneal injections are give table II The drug resembles mecamylamine in tissue d tion It is concentrated in tissues rich in nuclear m especially the kidney, spleen, liver, and lung Tissue/ concentration ratios are lower in the case of pempidine tha *mecamylamine, showing that there is less tissue affinity for* former drug This partly explains the more rapid excretio pempidine, since a greater fraction of any given dose within the extracellular space and is therefore available excretion The L D $_{50}$ of pempidine is considerably higher that of mecamylamine, the L D $_{50}$ of pempidine by int

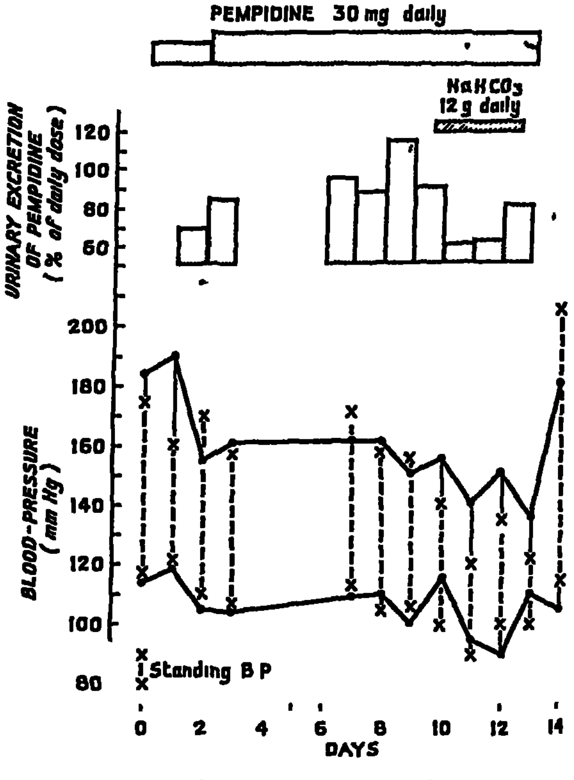


Fig 4—Effect of alkalinisation of the urine during treatment pempidine on the blood-pressure and urinary excretion of drug

TABLE II—TISSUE CONCENTRATIONS OF PEMPIDINE AND MECAMYLAMINE AFTER SUBLETHAL AND LETHAL INTRAPERITONEAL INJECTIONS IN RATS

Organ concerned	Pempidine		Mecamylamine	
	Concentration mg per kg wet tissue	Tissue/plasma concentration ratio	Concentration mg per kg wet tissue	Tissue/plasma concentration ratio
Sublethal injections *				
Brain	34 5	4 9	44	7 9
Heart	53	7 4	49	8 8
Liver	55	7 7	84	15 0
Lung	88	12 4	164	29 4
Kidney	113	16 0	117	21 0
Voluntary muscle	14	2 0	19	3 4
Spleen	108	15 2	118	21 2
Plasma	7 1	—	5 6	—
Erythrocytes	6 0	0 85	5 4	0 95
Lethal injections†				
Brain	66	1 02	40	1 8
Heart	106	1 64	82	3 8
Liver	236	3 5	90	4 0
Lung	220	3·4	150	6 8
Kidney	453	7 0	120	5 4
Voluntary muscle	78	1 2	37	1 7
Spleen	530	8 1	260	12 0
Plasma	65	—	22	—
Erythrocytes	70	1 03	22	1 15

* Sublethal injections (one hour after injection of drug, 16 mg free base per kg body-weight)

† Lethal injections (immediately before death after injection of mecamylamine, 60 mg base per kg body-weight, and pempidine 175 mg base per kg)

toneal injection is 175 mg per kg body-weight of active base, the corresponding L D $_{50}$ of mecamylamine is 44 mg per kg (Stone et al 1956) This higher lethal dose is confirmed by the greater concentrations of pempidine in all tissue after lethal injections of the drugs (table II) Concentrations in voluntary muscle and plasma are particularly important since muscle makes up about 33% of the body-weight and extracellular fluid about 20% Concentration of pempidine at death was 2 1 times that of mecamylamine in muscle and 3 0 times that in plasma Both drugs readily cross the blood-brain barrier and are found in relatively high concentration in the central nervous system The pharmacological effects of lethal doses of pempidine in rats are similar to those previously described for mecamylamine (Milne et al 1957) and include tremor and convulsions

Clinical Effects

Intravenous Dosage

21 patients were studied after single intravenous doses of pempidine In all except 2 cases the drug was given in a dose of 5 mg hydrochloride (4 mg base) After intravenous injection, given with the patient lying flat with the head on two pillows, the onset of action was rapid, a fall in blood-pressure being noted within two minutes in most cases The rapidity of onset of action was comparable with that after intravenous injection of pentolinium (fig 5) In some cases no fall in blood-pressure occurred in the recumbent position, but in all except 1, postural hypotension was present on standing ten to fifteen minutes after the dose In this case the patient did not respond to an intravenous dose of 5 mg, but a later oral dose of 20 mg produced a prolonged hypotensive effect

The duration of effect of a single intravenous dose, as judged by the presence of postural hypotension, was from two to six hours in patients with normal renal function The length of this period was not consistently altered in 11 patients whose urine had been made either acid or alkaline before administration of the drug

Oral Dosage

Single oral doses of 5–20 mg bitartrate (2 5–10 mg pempidine base) were given to 9 patients After an oral dose a hypotensive effect was usually observed within an hour, although in 2 cases the onset of action was delayed for three to four hours The total duration of hypotensive action was for six to seven hours after the dose, although the maximal effect lasted for only one to three hours

In 2 cases after an intravenous dose, and in 3 after a large oral dose, there was a severe fall in blood-pressure, and the effect of the drug was prolonged for as long as twenty-four to thirty-six hours One of these patients had severe oliguria which undoubtedly interfered with excretion of the drug

Continuous Oral Treatment

27 patients have been observed on continuous treatment with pempidine Initially the drug was administered thrice daily, but it was found that when the interval between doses was as long as eight hours, the blood-pressure tended to rise again two to three hours before the next dose Accordingly, it is now our practice to give the drug four times during the day, the doses being spaced at five-hourly intervals from 7 A M to 10 P M On this regime a sustained blood-pressure reduction may be obtained throughout the day If necessary the last dose at night has been doubled, thus giving a prolonged action during the night hours

In patients with impairment of renal function the drug need be given less frequently In 2 patients, with blood-urea levels of 80–100 mg per 100 ml, twice-daily dosage was sufficient to maintain a steady blood-pressure reduction

Type of Case Treated

Of the 27 patients who received continuous treatment with pempidine, 8 had malignant hypertension, with grade-IV fundi (Wagener and Keith 1939), 9 were classified in grade III, and 10 in grade II There were 10 males and 17 females, and their ages ranged from 30 to 66 5 patients had renal hypertension of varying ætiology, and 22 were diagnosed as essential hypertension

Duration of Treatment

In 24 patients treatment has been continued up to the time of writing for a period varying from two to twenty weeks (average ten weeks) Treatment was stopped after a short period in 3 patients in 1 case because of the presence of severe cerebrovascular disease, in 1, a schoolteacher, because of blurring of vision which interfered with her work, and in 1 because of persistence of head-

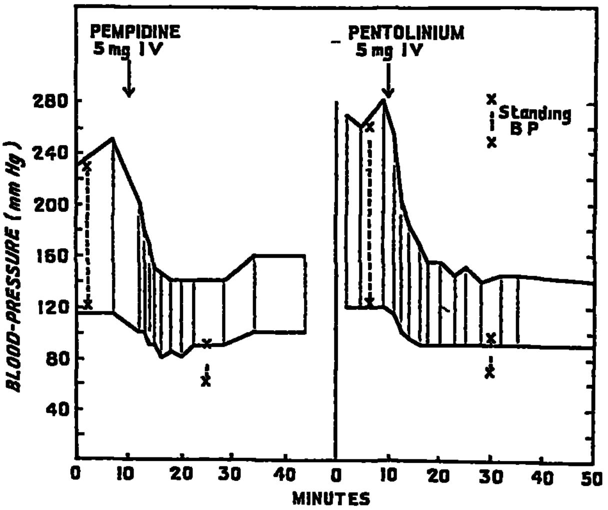
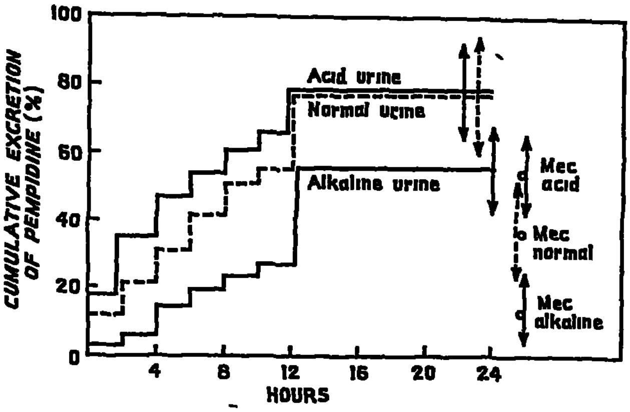


Fig 5—Effect of an intravenous dose of pempidine, compared with that of pentolinium, in a female, aged 53, with malignant essential hypertension



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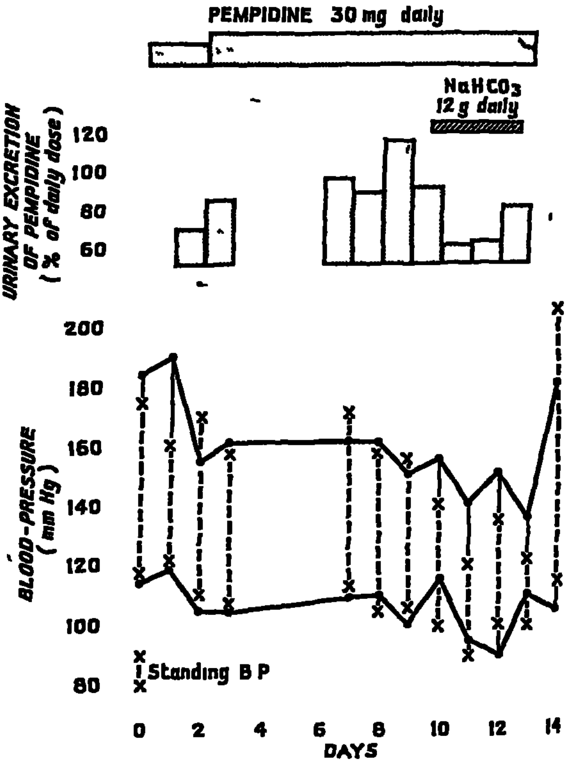

Fig 4—Effect of alkalinisation of the urine during treatment pempidine on the blood-pressure and urinary excretion of drug

TABLE IV—COMPARISON OF THE CHEMICAL PROPERTIES OF PEMPIDINE AND MECAMYLAMINE WITH THOSE OF CLOSELY RELATED AMINES

Reactions of Secondary Amines

Chemical reaction	Piperidine	2 : 2 : 6 : 6-tetramethylpiperidine	Mecamylamine
Reaction with carbon bisulphide and ammoniacal copper sulphate to form brown copper salts of dithiocarbamic acids	Strong Immediate	Weak Very slow	Weak Slow
Reaction with 1 : 2-naphthoquinone - 4 - sulphonic acid to form indophenol dyes	Strong Immediate	Nil	Nil
Reaction with sodium nitroprusside and acetaldehyde.	Strong Immediate	Very weak Very slow	Weak Slow

Reactions of Tertiary Amines

Chemical reaction	N-methylpiperidine	Pempidine	N-methylmecamylamine
Reaction with citric acid and acetic anhydride	Strong Rapid	Moderate Slow	Weak Slow

In its chemical properties, pempidine resembles mecamylamine more than the structurally more closely related amines, piperidine and N-methylpiperidine (table IV) I … on that the secondary amines 2 : 2
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in acid than alkaline urine, are concentrated in tissue containing a high proportion of cell nuclei, and easily cross the blood-brain barrier

Several differences in detail make pempidine a potentially more useful drug than mecamylamine The excretion of pempidine is more rapid, chiefly because of a lower tissue affinity for the drug Excretion of pempidine is less affected by variation in acid-base balance than that of mecamylamine The difference between an effective and a toxic concentration is probably greater in the case of pempidine

A steady hypotensive effect can be maintained throughout the day when pempidine is given orally at five-hourly intervals The dosage of pempidine can be quickly increased, owing to the rapid elimination of the drug

The chemical and physicochemical properties of pempidine and of mecamylamine in relation to their ganglion-blocking action are discussed

We gratefully acknowledge the encouragement given us by Prof J McMichael, F.R.S, and his help in the preparation of this paper Thanks are also expressed to Messrs May & Baker Ltd for supplies of pempidine ("Perolysen") and 2 : 2, 6 : 6-tetramethylpiperidine, and to Messrs Merck, Sharp & Dohme for supplies of mecamylamine and dimethylaminoisocamphane

REFERENCES

Allanby, K D, Trounce, J R. (1957) *Brit med J* ii, 1219
Baer, J E, Paulson, S F, Russo, H F, Beyer, K H (1956) *Amer J Physiol* 186, 180
Bennett, G, Tyler, C., Zaimis, E (1957) *Lancet*, ii 218
Brodie, B B, Udenfriend S (1945) *J biol Chem* 158, 705
Chargaff, E, Levine, C, Green, C. (1948) *ibid* 175, 67
Grant, A P, Boyd, J S (1957) *Lancet*, i, 713
Harington, M., Kincaid-Smith, P (1958) *ibid* i, 499
Lee, G E, Wragg, W R, Corne, S J, Edge, N D, Reading, H W (1958) *Nature, Lond* 181, 1717
Lockett, M F (1949) *Brit J Pharmacol* 4, 111
Milne, M D, Rowe, G G, Somers, K, Muehrcke, R C., Crawford, M A (1957) *Clin Sci* 16 599
— Scribner, B H, Crawford, M A. (1958) *Amer J Med* 24, 709
Norton, S, Phillips A P (1953) *Nature, Lond* 172, 867
Paton, W D M, Zaimis, E J (1952) *Pharmacol Rev* 4 219
Schneckloth, R E, Corcoran, A C., Dustan, H P, Page, I H (1956) *J Amer med Ass* 162, 868
Scribner, B H, Crawford M A, Dempster, J (1958) in preparation
Spinks, A, Young, E. H P (1958) *Nature, Lond* 181, 1397
Steudel, H (1932) *Z physiol Chem* 213, 11
Stone C A, Torchiana, M L, Navarro, A, Beyer, K H (1956) *J Pharmacol* 117, 169
Tillson, E. K, Paulson, S F, Beyer, K H (1954) *J Lab clin Med* 44, 880
Von Euler, U S (1945) *Acta pharmacol scand* 1 29
Wagener, H P, Keith, N M (1939) *Medicine, Baltimore*, 18, 317
Williams, R T (1947) Detoxication Mechanisms London

INFLUENZAL ENCEPHALOPATHY AND POSTINFLUENZAL ENCEPHALITIS

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… have recently been described (Dubowitz 1958,
… and Goodbody 1958, Compton Smith 1958,
… t al 1958) of encephalitis, both fatal and non-
… ciated with attacks of influenza-like illness
… ring at a time when Asian influenza was

… time that a virus antigenically similar to
… /57 caused an epidemic was in the winter
… according to Mulder and Masurel (1958),
… rom people born before that date neutralise
… a-virus hæmagglutinin, whereas sera taken
… 7 epidemic from younger persons do not

aches for which treatment had been instituted but which were not relieved by the drug.

Dosage

The dosage of pempidine required to produce an adequate hypotensive effect varied widely, a dose of 2.5 mg twice daily sufficing in one patient, whereas as much as 25 mg four times daily has been given in another case with only partial control of blood-pressure. This latter patient is also refractory to other ganglion-blocking drugs. The average total daily dose given as maintenance treatment in this series was 32.5 mg bitartrate (16 mg pempidine base).

Treatment was usually started with a dose of 2.5 mg q.i.d. It was found that the dose could be raised rapidly, increasing each dose by 2.5 mg daily until a satisfactory reduction in blood-pressure was achieved. Because of the rapid elimination of the drug from the body, it is therefore possible to reach a stable therapeutic dose level with reasonable safety in a few days—a procedure which would be fraught with danger in the case of mecamylamine.

Tolerance

In the limited period of study, no evidence has been seen of the development of "tolerance" to pempidine, analogous to that seen with hexamethonium and other quaternary ammonium compounds. In this respect the drug resembles mecamylamine.

Combination with Other Drugs

In 6 patients reserpine was added to the regime of treatment, and in 3 others a combination of chlorothiazide and reserpine was used in addition to pempidine. Preliminary observations suggest that these compounds potentiate the action of pempidine, as has been described with other hypotensive drugs.

Side-effects

The majority of patients in whom treatment with pempidine was maintained experienced some side-effects from the drug, the symptoms being similar to those usually observed during treatment with ganglion-blocking agents.

The side-effects ran parallel with the hypotensive action of the drug, coming on about half an hour after an oral dose, being at their maximum for one to two hours, and often wearing off before the next dose was due. Constipation was seen most frequently, in 18 out of 27 patients, together with dryness of the mouth (18) and blurring of vision (12). These symptoms were usually only mild or of moderate severity, in 3 patients, however, they were severe enough to be a major cause of complaint. Other symptoms were noted in a few patients, as follows: drowsiness (3), feeling of weakness (2), difficulty in micturition (2), diarrhœa (2), faintness (2), and a feeling of shakiness (1).

All side-effects disappeared rapidly on omitting the drug. This was particularly noticeable with constipation. 3 patients developed a syndrome of early paralytic ileus, with vomiting, abdominal pain, and distension, in each case these symptoms cleared completely in twelve hours after stopping pempidine. This is in marked contrast to experience with mecamylamine where a similar complication may take several days to clear—reflecting the relatively slow elimination of mecamylamine from the body.

Patients taking pempidine are instructed to try to ensure, with aperients if necessary, a bowel action before the first dose of the day. If constipation persists in spite of these measures, they are advised to omit one or two doses of the drug, a normal bowel action then occurs, and the drug is resumed in the evious dosage.

TABLE III—COMPARISON OF DOSAGE AND CLINICAL EFFECTS OF PEMPIDINE AND MECAMYLAMINE

Case	Pempidine			Mecamylamine		
	Daily dose (mg free base)	B P control	Side-effects	Daily dose (mg free base)	B P control	Side effects
1	20	Good	+	32	Good	+
2	45	Good	++	56	Good	+
3	10	Good	0	8	Good	0
4	10	Good	0	24	Fair	++
5	15	Good	±	36	Fair	+
6	17.5	Poor	++	64	Poor	+
7	50	Poor	+	48	Poor	+

B P = blood-pressure.

Comparison with Mecamylamine in Patients treated with Both Drugs

7 of the patients treated with pempidine had previously been receiving mecamylamine for at least twelve months, so that a direct comparison of the dosage and clinical effects of the two drugs was possible in these cases (table III). The dose of pempidine, expressed as the free base, which was effective in controlling blood-pressure was smaller (average 60%) than that of mecamylamine. There was little to choose between the two drugs in respect of side-effects, which were more prominent with pempidine in 2 patients, and in 2 with mecamylamine.

Discussion

Pempidine is similar in many respects to mecamylamine. Both drugs are rapidly and completely absorbed from the gut. They readily cross cell membranes and are concentrated within tissues by intracellular protein-binding, especially to nucleoproteins. The excretion of both drugs is influenced by urinary pH, clearance being decreased in alkaline and slightly increased in acid urine. This type of excretion depends on diffusion across the renal tubular cell membranes and has recently been reviewed by Milne et al. (1958).

There are, however, important differences in detail which may make pempidine a more useful antihypertensive agent than mecamylamine. While 25% of mecamylamine is bound to plasma-protein, pempidine is not so bound, and therefore all the drug in plasma is pharmacologically active. Pempidine is excreted more rapidly than mecamylamine. This is partly due to lower tissue affinity for pempidine, and partly to higher clearance-rates of pempidine as compared with mecamylamine in alkaline or weakly acid urine (Scribner et al. 1958). More rapid excretion is advantageous because toxic accumulation of the drug in the body is less likely. In addition, the dosage of pempidine can safely be increased to effective levels more rapidly than mecamylamine. Although the excretion of both drugs is influenced by change in urinary pH, variation in mecamylamine excretion is greater than that of pempidine. The hypotensive effect of pempidine is therefore less variable despite changes in acid-base balance.

The L.D.$_{50}$ of pempidine in mice is three to four times higher than that of mecamylamine (Corne and Edge, personal communication, Spinks and Young 1958). The effective dosage of pempidine in hypertension in man is usually lower than that of mecamylamine. There is probably therefore a greater margin between an effective therapeutic and a toxic dose in the case of pempidine. These preliminary results make it probable that any observed pempidine toxicity will be both less severe and briefer than that complicating mecamylamine therapy. Much longer experience will be necessary before the relative value of the two drugs in actual clinical practice can be finally established.

inflammatory cells was noted Detailed histological studies are being done but are not yet ready

GROUP 2

Four patients, aged 2, 7, 10, and 46

Case 2 —A man, aged 46, employed in a chocolate factory, was admitted on Oct 2, 1957 4 days before admission he had had "flu", he went back to work 2 days later On the day of admission he became increasingly mentally peculiar By 10 P M that day he was comatose but would grasp at objects put into his hands with a peculiar coarse tremor Next day he was deeply comatose, not responding to stimuli, and having a succession of fits His C S F contained 188 cells per c mm, (130 erythrocytes, 45 lymphocytes, and 13 polymorphs), protein was 111 mg per 100 ml, sugar 72 mg, and chloride 670 mg There were no localising physical signs His temperature was unstable, fluctuating up to 104 8°F He was treated with paraldehyde and corticotrophin, and with streptomycin as for tuberculous meningitis His temperature fell on the 3rd day after admission, and he looked much better 2 days later he was conscious again, the day after that a red rash, almost varicelliform, appeared on his back across his shoulders but not elsewhere It had disappeared 2 days later, when he was almost normal mentally though he still seemed a bit dazed On Oct 11 his C S F contained protein 42 mg per 100 ml, no globulin, 6 lymphocytes, 1 polymorphonuclear leucocyte, and 107 erythrocytes per c mm A Lange test showed 1,1,1,1,0,0,0,0,0,0 He made a complete recovery

Complement-fixation tests against influenza-A antigen gave titres of 1 64 and 1 64+ on sera taken 2 days after admission and 14 days later The C S F was inoculated into eggs and tissue cultures of HuL1 cells, no virus was isolated Complement-fixation tests for the other antigens and the Paul-Bunnell test were negative Fæces were unfortunately not available in the acute stage

At least three of these patients showed instability of the temperature-regulating mechanism One child, aged 2, recovered very slowly and was left with some residual spasticity All were treated in the acute state with corticosteroids of one kind or another, and all but one recovered rapidly

GROUP 3

Two males—one aged 2 years 8 months, the other aged 39 The onset was 11 days and 7 days respectively after an attack of clinical influenza

Case 3 —The boy was admitted to the Children's Hospital on Oct 21 with 3 days' history of malaise and constipation, 2 days' history of crying at night On admission all his reflexes were found diminished, Kernig's sign was positive, the back, but not the neck, was stiff A white cell count showed 15,400 per c mm (polymorphs 54%) His C S F contained 50 cells per c.mm (lymphocytes 90%), sugar 82 mg per 100 ml, and protein 260 mg No virus was isolated from the fæces Complement fixation for poliomyelitis was negative on two samples of serum taken 10 days apart, both gave a positive complement fixation for influenza-A soluble antigen at 1 32+ Paralysis spread upwards from below Partial respiratory paralysis was treated by positive-pressure respiration, treatment with corticoids was associated with recovery of movement from above downwards The child made a complete recovery with no residual paralysis At no time was there detectable sensory impairment

Case 4 —A radio engineer, aged 39, had "flu" early in October and returned to work 4 days after the onset 3 days later he felt tired and developed weakness of his legs and difficulty in walking and micturition 2 weeks later he noticed weakness in his arms, and he was admitted to hospital on Oct. 14 He was now febrile and had no reflexes or power of movement in his legs, his arms were weak, and he showed some nystagmus His C S F contained 200 erythrocytes and 200 leucocytes (lymphocytes 80%), protein was 445 mg per 100 ml, sugar 51 mg, and chloride 654 mg Pandy ++, Lange 0,0,0,1,2,2,2,1,0,0 His hæmoglobin was 95%, and the white-cell count 19,000 per c mm (polymorphs 87%) There was no sensation to pinprick below T 3, and no sensation to touch below T 6 Lung expansion was poor, only the diaphragm working

Next day respiration became weaker, a tracheotomy was done, and he was placed in a respirator His eye movements became limited, bilateral facial weakness appeared, and his tongue was protruded to the left Cortisone therapy was started and maintained for 4 weeks 10 days later the cranial nerves were normal and arm movement improved Over the next few days his breathing improved and he was independent of the respirator for long periods His left ankle and knee jerks returned, and his plantar responses became extensor A severe bedsore, however, persisted, and after 6 weeks in hospital he became ill and died 2 days later of bronchopneumonia

Sera taken on admission and 14 days later both gave a complement-fixation titre of 1 32 for influenza A Egg and tissue cultures inoculated with C S F and throat washings yielded no virus The cortisone treatment may well have prevented a rise in the complement-fixation titre after admission

Postmortem Findings —Patchy bronchopneumonic consolidation was found in both lungs The brain was fixed whole Histologically, perivascular demyelination was found, it was greatest in the cord, areas of demyelination being so extensive as to become confluent In the medulla the lesions were not so extensive, but one confluent area of demyelination almost surrounded one olivary nucleus Lesions were numerous in the cerebellar peduncles, especially in the middle peduncle, and were also found in the white matter near the lateral wall of the ventricle near the hippocampus major Fat-filled macrophages were seen in and around the perivascular spaces All the lesions appeared to be at about the same stage

This clinical history and the histological findings resemble closely Greenfield's (1930) second case

GROUP 4

This group comprises cases presenting with a history of an influenza-like illness followed, after an interval of a few days, by neurological illness, and where complement-fixation tests or hæmagglutination-inhibition tests, or both, for influenza remained persistently negative, and cases where the diagnosis of influenza was in doubt, or where some possible cause other than influenza was discovered There were six such patients, aged 3, 5, 6, 32, 50, and 50

Case 5 —A boy, aged 5, had headache, abdominal pain, lassitude and drowsiness a week before admission His mother noticed that he had some muscular stiffness On admission on Nov 11, 1957, his temperature was 99 4°F and his pulse-rate 120 He was apathetic, with generalised muscular rigidity His plantar reflexes became extensor but reverted to normal 5 days later His C S F contained 9 leucocytes per c mm and a slight increase in protein The muscular rigidity gradually subsided, and the boy went home

No virus was isolated from C S F or fæces, but the complement-fixation titre for influenza rose from 1 64 on serum taken soon after admission to 1 128 on convalescent sera However, poliovirus type 1 was isolated from the fæces of his cousin, aged 6, who was admitted the following day, also with 3 days' history of drowsiness, abdominal pain, and headache No paralysis developed, and he was discharged on Dec 2, in good condition Complement-fixation titres against influenza A were the same as for his cousin Influenza virus was not grown from throat swabs in either case The complement-fixation test against poliovirus heated antigen remained negative

Acute hæmorrhagic leucoencephalitis was found in only one patient post mortem Serum was unfortunately not

(Clarke et al (1958) and Henle et al (1958) have reservations about this) Accordingly we looked through some of the German and English medical journals for 1890 (the *Deutsche medizinische Wochenschrift*, *Virchows Archiv*, the *British Medical Journal*, and *The Lancet*) to see whether there was any mention of acute encephalitis associated with, or as a sequel to, clinical influenza, but we found no such case recorded, though Crome (1954) had earlier noted three reports of it in the German literature of 1892 In more recent years, however, some authors have described an association between clinical influenza and either encephalitis or the Guillain-Barré syndrome In most cases laboratory confirmation of influenza-virus infection, either by isolation or by serological methods, was lacking

Greenfield (1930) described two cases of encephalitis Holmes (1947) described six cases of atypical pneumonia, of which two were associated with polyneuritis, three with lymphocytic meningitis, and one with encephalitis Hollander (1947) reported twenty-three cases of sensory polyneuritis, of which seventeen had an influenza-like illness 1–3 weeks before onset, and two had congestion of the fauces Leigh (1946) described nine cases of encephalitis, myelitis, or polyneuritis occurring during an epidemic of influenza B More recently, cases with serological evidence of influenza A have been reported by Jennings (1952), who reported two cases of severe polyneuritis and a case of lymphocytic meningitis following attacks of influenza A Ferraro and Roizin (1957) have published a useful general review of postinfective encephalitis, and Crome (1954) gives a good review of the older literature on encephalitis associated with influenza

We have collected a number of cases where influenza-virus infection has been associated with neurological disturbance of various kinds Most occurred during the autumn epidemic, but a few occurred early this year These fell into four groups

Group 1—Fatal cases with a history of convulsions or fits or clinical "encephalitis" at the height of an attack of influenza, associated with a very congested brain at necropsy The diagnosis was confirmed by isolation of Asian-type virus from the lungs, and in one case from the brain as well When the illness had lasted 6 or 7 days, complement fixation to a titre of 1 8–1 16 could usually be got with influenza-A soluble antigen and postmortem serum Attempts to isolate virus from the lungs failed in one case but the naked-eye and histological appearance of the lungs was typical of influenza, and the necropsy was carried out more than twenty-four hours after death

Group 2—A history of encephalitis with onset from 3 days to 2 weeks after an attack of influenza In its most dramatic form this presented as confusion proceeding to coma, with flaccid limbs and little or no response to stimuli Diagnosis was made by demonstration of a high complement-fixing titre (a rise from 1 64 to 1 128 being found in one case) or by the presence, after recovery, of antibodies inhibiting hæmagglutination by Asian influenza virus, or both

Group 3—Cases presenting with ascending sensory and motor disturbance of the Guillain-Barré type

Group 4—Misleading cases

Laboratory Investigations

Sera were put up at a dilution of 1 4 against heated poliomyelitis-virus antigens (types 1, 2, and 3) and at a dilution of 1 8 against mumps soluble and viral antigens, influenza A, B, and C soluble antigens, psittacosis-group antigen, Q-fever antigen, and adenovirus antigen

For the hæmagglutination-inhibition test sera were treated with trypsin according to the method of Sampaio and Isaacs (1953) to destroy non-specific inhibitor Sera inhibiting 50% hæmagglutination of 1% human group-O cells by four agglutinating doses to an initial dilution of 1 16 or greater were regarded as affording evidence of past infection

Brain suspensions, 20% in saline solution, were made of a pool of pieces taken from cortex, white matter, basal ganglia, cerebellum, and medulla Brain and fæcal suspensions were inoculated into cultures of human-embryo liver-cells, the HuLi line established by Westwood et al (1957) was used, its sensitivity to polioviruses and adenoviruses is very similar to that of HeLa cells It is not susceptible to ECHO virus type 9 Brain and fæces from our most recent case was inoculated also into their MK 1 line of rhesus kidney-cells, which are readily susceptible to ECHO viruses

Influenza virus was isolated from 10–20% lung and/or trachea suspensions in saline-broth in 12–13-day-old eggs by the amniotic route in the usual way Where the morbid anatomical appearances strongly suggested influenza, egg cultures were usually positive where necropsy was done within 24 hours of death, and usually negative after that time, but on one occasion influenza virus was isolated about 44 hours after death

Histological preparations were made of some pieces of brain, but most of the material is still undergoing the lengthy neuropathological embedding

Illustrative Case-reports

One case-history typical of each group will be given in detail, significant aberrations from this pattern will be mentioned where necessary

GROUP 1

Six patients, aged 3½, 4, 11, 12, 30, and 44, two children were siblings

Case 1—A boy, aged 11 Developed influenza in September, 1957 He vomited copiously 4 days later and he became delirious the following day On admission to Little Bromwich Hospital 6 days after the onset he was stuporous, with cerebral irritability and a mild left facial paresis tendon-reflexes were brisker than normal, and both plantar responses were extensor A clinical diagnosis of influenzal encephalitis was made His cerebrospinal fluid (C S F) contained less than 1 cell per c mm , protein was 10 mg per 100 ml , and chloride 770 mg He rapidly became comatose and died the day after admission

Postmortem Findings—At necropsy 44 hours after death (the body having been refrigerated) the trachea showed acute inflammation, with a little thin pus within the lumen The lungs showed patchy consolidation, with only a few areas of hæmorrhage The brain appeared soft, swollen, and friable, with intense congestion of the surface vessels On section, the vessels of the white matter were found to be dilated, but there were no macroscopic hæmorrhages Influenza virus of the Asian type was isolated from a tracheal swab, though not from brain or lung Tissue cultures inoculated with suspensions of fæces and brain remained healthy

The two youngest patients presented with convulsions as the only cerebral complication From the one aged 3½, influenza virus was isolated both from the brain suspension and from a pool of lung and trachea, but the brain suspension yielded no virus when diluted 1 10, whereas virus grew in 4/4 eggs inoculated with a dilution of 1 1000 (the highest dilution tested) of the lung and trachea suspension It is not unreasonable to suspect that the pieces of brain may have been contaminated with virus in the postmortem room, because no precautions were taken to prevent this, or there may well have been virus present in the blood-stream Histological examination of a few blocks revealed no gross changes in the brains from any of these cases, no perivascular infiltration with isolated from cases in group 1 at the end of the epidemic and convalescent sera from their relatives were compared by the hæmagglutination-inhibition technique with convalescent sera and viruses isolated from uncomplicated cases of influenza in the Midlands at the beginning of the epidemic The viruses in each case had had one amniotic and two allantoic passages Eight strains of virus and eight sera were put up against each other in a " chess-board " type of experiment No differences outside the limits of experimental error were found between any of the viruses

The ætiological association of influenza, at a time when the infection was so widespread, with encephalitis or myelitis in groups 2 and 3 seems less certain Although a case could be made out for it, we feel that the evidence for a direct connection is insufficient This observation is supported by the cases in group 4 Furthermore, it is not rare to elicit a history of respiratory infection or of pyrexia preceding by a few days the onset of encephalitis occurring at times when epidemic influenza is not prevalent.

We endorse the remark of Dunbar et al (1958) that more evidence is needed

Summary

Cases are described of encephalopathy, encephalitis, or ascending paralysis associated with Asian-type influenza-virus infection The diagnosis of influenza was supported by isolation of the virus or by serological means

Cases clinically simulating postinfluenzal encephalitis, where serological tests for influenza remained negative in convalescence, or where another possible cause of encephalitis was found, are also described

An attempt is made to assess the significance of positive serological findings for influenza in cases of encephalitis at a time of epidemic spread

It is concluded that, though the hypothesis is attractive, the ætiological relationship between influenza-virus infection and " postinfluenzal encephalitis " is not proven

We wish to thank Prof W Melville Arnott, Dr R D Blachford, Dr R Fothergill, Dr J M Garvie, Dr M Jefferson, Dr A C Kendall, Dr F L Ker, Dr J C Macaulay, Dr Clifford Parsons, Dr W Carey Smallwood, Dr S R F Whittaker, and Mr J A Williams for permission to mention their patients and for details of case-records, to Dr W H J Baker, Dr W T Smith, and Dr A L Woolf for details of postmortem and histological findings, and to Mr N E Chard and Mr J R Foster for most of the serological work and virus isolations We are indebted to Messrs Lederle, Inc , for the diagnostic antigen for Q fever, and to Dr J C N Westwood and Dr F Sheffield, for the cultures of MK 1 and HuLı cells Prof C H Stuart-Harris kindly read our draft and drew our attention to Dr Crome's paper

REFERENCES

Balducci, D , Tyrrell, D A J , Stuart-Harris, C H (1956) *Arch ges Virusforsch* 7, 28
Clarke, S K R , Heath, R B , Sutton, B M , Sutton R. N P , Stuart-Harris, C. H (1958) *Lancet* i, 814
Crome, L. (1954) *Mschr Psychiat Neurol* 128, 159
Dubowitz, V (1958) *Lancet*, i, 140
Dunbar J M , Jamieson, W M , Langlands, J H. M , Smith, G H (1958) *Brit med J* i, 913
Ferraro, A., Roizin, L (1957) *J Neuropath* 16, 423
Greenfield, J G (1930) *J Path Bact* 33, 453
Henle, W , Lief, F S , Fabiyi, A (1958) *Lancet*, i, 818
Hollander, E (1947) *N Y St J Med* 47, 1378
Holmes, J M (1947) *Brit med J* i, 218
Jennings, G H (1952) *ibid* i, 123
Leigh, A. D (1946) *ibid* ii, 936
McGill, R J , Goodbody, R A (1958) *Lancet*, i, 320
Mulder, J , Masurel, N (1958) *ibid*, p 810
Sampaio, A. A C , Isaacs, A (1953) *Brit J exp Path* 34, 152.
Smith R. N C. (1958) *Lancet*, i, 217
Westwood J C N , Macpherson, I A , Titmuss, D H J (1957) *Brit J exp Path* 38, 138

NEUROLOGICAL DISORDERS ASSOCIATED WITH ASIAN INFLUENZA

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REPORTS of disorders of the nervous system during epidemics of influenza have appeared from time to time (Leigh 1946, Holmes 1947, Jennings 1952) Following the recent epidemic of influenza A (Asian), Dubowitz (1958) reported 2 cases, and further examples were given by Compton Smith (1958) and McGill and Goodbody (1958) In few cases, however, have laboratory studies adequately established that influenza was the primary disorder

During October and November we saw 4 patients in whom neurological disorders followed a febrile illness suggestive of influenza We here report these cases and give details of influenza-A (Asian) antibody titres

Case-reports

Case 1—A boy, aged 16, was admitted to the Cardiff Royal Infirmary on Nov 20, 1957 Nine days previously he had felt unwell, with headache, muscle pains, fever, and cough He was seen by his family doctor, who diagnosed Asian influenza His symptoms persisted for three days On the fourth day his fever subsided and he felt better On the evening of the fifth day his headache returned and he started to vomit Headache and vomiting increased in frequency and severity until the eighth day, when he became drowsy and was admitted to a local hospital He was transferred to the Cardiff Royal Infirmary next day

He was drowsy, irritable, uncooperative, and unable to understand or carry out simple instructions There were no involuntary movements The temperature was 98 6°F, pulse-rate 90 per minute, respiration-rate 18 a minute There was slight neck rigidity No abnormality was detected in the cranial nerves In the extremities there was slight reduction in muscle power in the left arm and leg but the tone was normal on both sides Voluntary movements of both upper limbs were poorly carried out Sensation to pin-prick and cotton-wool was normal Tendon reflexes were present and symmetrical, but the plantar responses were extensor There were no abnormal signs in other systems

Investigations—Lumbar puncture on the day of admission yielded a clear cerebrospinal fluid under a pressure of 70 mm H_2O cells, less than 5 lymphocytes per c mm , protein 20 mg per 100 ml , chloride 138 mEq per litre, sugar 80 mg per 100 ml

The blood-count was normal A radiograph of the chest revealed no abnormality An electroencephalogram on the day after admission showed a grossly abnormal record, with high-voltage slow delta waves and a little theta activity in all leads (fig 1)

Complement-fixing antibodies for influenza A produced a titre of 1/1024 (Nov 20) and 1/256 (Dec 2 and 5) By hæmagglutination inhibition the titre on Nov 20 was 1/512 for the Asian variety and less than 1/4 for the Scandinavian, Eire, and Dutch strains

Progress—His condition remained unchanged for about thirty-six hours and then steadily improved By Nov 25 he was fully alert, cheerful, talkative, and free from symptoms He had complete amnesia for events between Nov 12 and 23 The electroencephalogram taken on Nov 25 was normal

Case 2—The 13-year-old sister of the boy in case 1 was admitted to the Cardiff Royal Infirmary on the same day She taken before death or at necropsy, and no virus was isolated from lungs, central nervous system or fæces, but a respiratory infection was suggested by the following case

Case 6—A woman, aged 33, complained of cough, general malaise, and tiredness a week before admission The day before admission she vomited and could not sleep at night On the day of admission (Nov 5, 1957) she complained of weakness of her right arm and leg and subsequently became incontinent and stuporous Her temperature was 101°F, and she was having frequent convulsions All her tendon-jerks were exaggerated, her plantar responses was extensor, and she had bilateral ankle clonus Lumbar puncture yielded hazy C S F containing 1000 polymorphs and 30 lymphocytes per c mm, protein 228 mg per 100 ml, sugar 51 mg, and chloride 760 mg Convulsions persisted next day, and she died that afternoon At necropsy her brain was swollen and congested. On section very many small petechial hæmorrhages were found involving the white matter of the cerebral hemispheres almost exclusively, though the brain-stem on the right side showed similar lesions Histologically "ring hæmorrhages", with much perivascular infiltration with many polymorphs and some lymphocytes, were found Acute tracheitis was present and the trachea contained pus, but the lungs histologically showed no gross abnormality—certainly nothing to support a diagnosis of epidemic influenza Influenza virus was not isolated from brain or lung, and no cytopathogenic virus was isolated in tissue culture from brain, lung, or fæces

It is possible, but by no means certain, that this was a case of influenza-virus infection, if so, the lungs returned to histological normality remarkably rapidly It seems more likely that the tracheitis was due to something other than Asian influenza

The next case presented a similar history but the patient recovered completely

Case 7—A man, aged 50, complained of shivering and pains in the back This was on Jan 1, 1958, at a time when some Asian-type virus was being isolated in the Midlands, and a diagnosis of influenza was made Next afternoon he was found comatose, but consciousness returned gradually over the next 4 days His C S F contained 20 lymphocytes per c mm, protein was 80 mg per 100 ml, chloride 720 mg, and sugar 71 mg The complement-fixation test for influenza remained negative in convalescence, the only positive finding being a titre of 1 32 with both acute and convalescent sera against herpes simplex virus, with a mouse-brain antigen prepared according to Balducci et al (1956)

Three other patients presented with encephalitis-like symptoms following attacks of "influenza", oculomotor disturbances were common to all three, and all gave negative complement-fixation tests, and, in the two cases where they were done, negative hæmagglutination-inhibition tests also

Case 8—A man, aged 50, became confused, diplopic, and unsteady after "quite typical flu" in mid-September, 1957 His diplopia lasted only about 24 hours, but 6 weeks later, when he was seen as an outpatient, he was still unsteady, felt weak, and had trouble with his memory He was slightly dysarthric and had mild lateral nystagmus and intention tremor His gait was severely ataxic He slowly improved after this and when last seen was much better though not ready to return to work Complement-fixation and hæmagglutination-inhibition tests were negative

Discussion

The problem is whether encephalitis associated with influenza is caused in some way, directly or indirectly, by the influenza virus, or whether the relationship is a chance one During an epidemic such as last autumn's usually cases are seldom referred to a laboratory unless they have features of special interest or the diagnosis is in doubt Among the cases reported here are some where the association of clinical "influenza" with encephalitis was misleading, and less notice may well have been taken of influenza following encephalitic symptoms than of encephalitis following influenza All the cases reported here have been "selected" in this respect by the clinician or pathologist, and a statistical analysis of them would obviously not be valid

Serological evidence has been adduced by ourselves and also by others (Dubowitz 1958, Dunbar et al 1958, and others) to support the diagnosis of influenza-A virus infection in association with encephalitis Now most of these cases occurred during the epidemic spread of a virus in an almost uniformly susceptible "virgin" population It would be interesting to know what proportion of the population as a whole would have given a positive complement fixation when the epidemic had just subsided—the time when convalescent sera were taken from most of the cases under discussion Most of the sera submitted to the Regional Virus Laboratory at this time gave a positive result, but most of them were from patients with a history of "flu", and so were not representative

Other evidence was sought Dunbar et al (1958) estimated that clinical influenza affected 20% of the population, but among those admitted to hospital for any reason the infection-rate (clinical and subclinical) was probably much higher than that

In a residential school for children with damaged hearts only four of about fifty children escaped illness The fact that the temperatures of all the children in the school are taken twice daily as a routine made detection of minor illness easier Though some children had slight pyrexia for only 24 hours, their complement-fixation tests nevertheless became positive

Sera were taken in December from all the forty-two children operated on for appendicitis in the Children's Hospital, Birmingham, in September, October, and November Hæmagglutination-inhibiting antibodies to Asian influenza were found in forty Of fifty-two sera taken at random from children attending as outpatients at that hospital thirty-five had similar evidence of past infection, so had thirteen of twenty adults attending as outpatients at Little Bromwich Hospital Presumably most of these patients acquired their infection during the epidemic It therefore seems that a convalescent serum from anybody admitted to hospital, from whatever cause, during the epidemic would have had a good chance of giving a positive complement-fixation test for influenza Of a much larger series collected in Sheffield after the epidemic Clarke et al (1958) found that 44% of the population had neutralising antibodies after the epidemic, though 56% of those aged 0–10 years and 70% of those aged 10–20 gave evidence of infection In view of the very good chance of catching influenza in hospital during an epidemic, our figures agree reasonably well with those of Clarke et al (1958)

The association of influenza with the cerebral symptoms and postmortem findings in group 1 is quite clear Whether it is necessary to invoke a specific toxic or infectious action of the virus seems doubtful We could not say confidently that all the changes seen could not have been produced by the severe anoxæmia and venous congestion associated with a hæmorrhagic pneumonia persisting for several days "Encephalopathy" seems a more appropriate term than "encephalitis"

To see whether there was anything unusual about viruses from "encephalopathic" cases, strains of virus isolated from cases in group 1 at the end of the epidemic and convalescent sera from their relatives were compared by the hæmagglutination-inhibition technique with convalescent sera and viruses isolated from uncomplicated cases of influenza in the Midlands at the beginning of the epidemic. The viruses in each case had had one amniotic and two allantoic passages Eight strains of virus and eight sera were put up against each other in a "chess-board" type of experiment. No differences outside the limits of experimental error were found between any of the viruses

The ætiological association of influenza, at a time when the infection was so widespread, with encephalitis or myelitis in groups 2 and 3 seems less certain Although a case could be made out for it, we feel that the evidence for a direct connection is insufficient This observation is supported by the cases in group 4 Furthermore, it is not rare to elicit a history of respiratory infection or of pyrexia preceding by a few days the onset of encephalitis occurring at times when epidemic influenza is not prevalent.

We endorse the remark of Dunbar et al. (1958) that more evidence is needed

Summary

Cases are described of encephalopathy, encephalitis, or ascending paralysis associated with Asian-type influenza-virus infection The diagnosis of influenza was supported by isolation of the virus or by serological means

Cases clinically simulating postinfluenzal encephalitis, where serological tests for influenza remained negative in convalescence, or where another possible cause of encephalitis was found, are also described

An attempt is made to assess the significance of positive serological findings for influenza in cases of encephalitis at a time of epidemic spread

It is concluded that, though the hypothesis is attractive, the ætiological relationship between influenza-virus infection and "postinfluenzal encephalitis" is not proven.

We wish to thank Prof W Melville Arnott, Dr R. D Blachford, Dr R Fothergill, Dr J M Garvie, Dr M Jefferson, Dr A. C Kendall, Dr F L Ker, Dr J C Macaulay, Dr Clifford Parsons, Dr W Carey Smallwood, Dr S R F Whittaker, and Mr J A Williams for permission to mention their patients and for details of case-records, to Dr W H J Baker, Dr W T Smith, and Dr A L Woolf for details of postmortem and histological findings, and to Mr N E Chard and Mr J R. Foster for most of the serological work and virus isolations We are indebted to Messrs Lederle, Inc., for the diagnostic antigen for Q fever, and to Dr J C N Westwood and Dr F Sheffield, for the cultures of MK 1 and HuLi cells Prof C H Stuart-Harris kindly read our draft and drew our attention to Dr. Crome s paper

REFERENCES

Balducci, D , Tyrrell, D A. J , Stuart-Harris, C. H. (1956) *Arch ges Virusforsch* 7, 28

Clarke, S K. R., Heath, R. B , Sutton, B M., Sutton R. N P , Stuart-Harris, C. H (1958) *Lancet* i, 814

Crome, L. (1954) *Mschr Psychiat Neurol* 128, 150

Dubowitz, V (1958) *Lancet*, i, 140

Dunbar J M., Jamieson, W M., Langlands, J H. M., Smith, G H (1958) *Brit med J* i, 913

Ferraro, A., Roizin L. (1957) *J Neuropath* 16, 423

Greenfield J G (1930) *J Path Bact* 33, 453

Healy, W Lief F S., Fabiyi, A. (1958) *Lancet*, i, 819

Hollander, E. (1947) N Y St J Med 47, 1378

Holmes, J M. (1947) *Brit med J* i, 218

Jennings, G H. (1952) *ibid* i 123

Leigh A D (1946) *ibid* ii, 936.

McGill, R. J , Goodbody R. A (1958) *Lancet*, i, 320

Mulder J, Masurel N (1958) *ibid* p 810

Sampaio A. A. C., Isaacs A. (1953) *Brit J exp Path* 34, 152.

Smith R. N. C. (1958) *Lancet*, i, 217

Westwood J. C. N , Macpherson, I A., Titmuss, D H. J (1957) *Brit J exp Path* 38, 138

NEUROLOGICAL DISORDERS ASSOCIATED WITH ASIAN INFLUENZA

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REPORTS of disorders of the nervous system during epidemics of influenza have appeared from time to time (Leigh 1946, Holmes 1947, Jennings 1952) Following the recent epidemic of influenza A (Asian), Dubowitz (1958) reported 2 cases, and further examples were given by Compton Smith (1958) and McGill and Goodbody (1958) In few cases, however, have laboratory studies adequately established that influenza was the primary disorder

During October and November we saw 4 patients in whom neurological disorders followed a febrile illness suggestive of influenza We here report these cases and give details of influenza-A (Asian) antibody titres

Case-reports

Case 1—A boy, aged 16, was admitted to the Cardiff Royal Infirmary on Nov 20, 1957 Nine days previously he had felt unwell, with headache, muscle pains, fever, and cough He was seen by his family doctor, who diagnosed Asian influenza. His symptoms persisted for three days On the fourth day his fever subsided and he felt better On the evening of the fifth day his headache returned and he started to vomit Headache and vomiting increased in frequency and severity until the eighth day, when he became drowsy and was admitted to a local hospital He was transferred to the Cardiff Royal Infirmary next day

He was drowsy, irritable, uncooperative, and unable to understand or carry out simple instructions There were no involuntary movements The temperature was 98 6°F, pulse-rate 90 per minute, respiration-rate 18 a minute There was slight neck rigidity No abnormality was detected in the cranial nerves In the extremities there was slight reduction in muscle power in the left arm and leg but the tone was normal on both sides Voluntary movements of both upper limbs were poorly carried out. Sensation to pin-prick and cotton-wool was normal Tendon reflexes were present and symmetrical, but the plantar responses were extensor There were no abnormal signs in other systems

Investigations—Lumbar puncture on the day of admission yielded a clear cerebrospinal fluid under a pressure of 70 mm H_2O cells, less than 5 lymphocytes per c.mm., protein 20 mg per 100 ml , chloride 138 mEq per litre, sugar 80 mg per 100 ml

The blood-count was normal A radiograph of the chest revealed no abnormality An electroencephalogram on the day after admission showed a grossly abnormal record, with high-voltage slow delta waves and a little theta activity in all leads (fig 1)

Complement-fixing antibodies for influenza A produced a titre of 1/1024 (Nov 20) and 1/256 (Dec 2 and 5) By hæmagglutination inhibition the titre on Nov 20 was 1/512 for the Asian variety and less than 1/4 for the Scandinavian, Eire, and Dutch strains

Progress—His condition remained unchanged for about thirty-six hours and then steadily improved By Nov 25 he was fully alert, cheerful, talkative, and free from symptoms He had complete amnesia for events between Nov 12 and 23 The electroencephalogram taken on Nov 25 was normal

Case 2.—The 13-year-old sister of the boy in case 1 was admitted to the Cardiff Royal Infirmary on the same day She

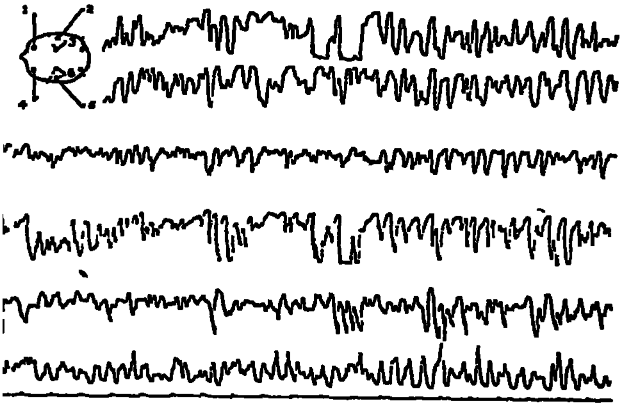


Fig 1—Case 1 electroencephalogram, Nov 21

ad been taken ill at the same time as her brother and her llness followed the same course She became drowsy on ov 18 and next morning was semicomatose She was admitted o a local hospital in coma and was transferred to the Cardiff oyal Infirmary next day

She was in deep coma There were no involuntary movenents Temperature 101 6°F, pulse-rate 100, respiration-rate 5 a minute The pupils were dilated and fixed to light The undi were normal The limbs were flaccid with symmetrically iminished tendon reflexes Both plantar responses were xtensor There was no response to painful stimuli No bnormal signs were detected in the cardiovascular or respiraory systems

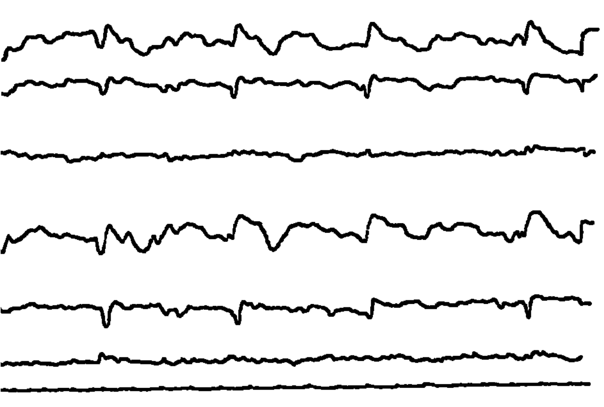
Investigations —Lumbar puncture on the day of admission roduced a clear colourless fluid under a pressure of 90 mm I_2O cells < 5 per c mm , protein 39 mg per 100 ml , chloride 24 mEq per litre, sugar 99 mg per 100 ml

Hb 15 5 g per 100 ml , leucocyte-count 11,800 per c mm 91% polymorphs) Platelet-count on Nov 25, 65,000 per mm , Dec 5, normal A radiograph of the chest revealed no bnormality

An electroencephalogram (Nov 21) showed a grossly bnormal record The tracing was very flat, but occasional low subdelta waves occurred exhibiting bilateral frontal preominance During part of the record the slow activity showed definite periodicity (fig 2) A further electroencephalogram n Nov 27 was normal

The titre of complement-fixing antibodies for influenza A as 1/2408 (Nov 20), 1/128 (Dec 2) and 1/64 (Dec 5) By emagglutination inhibition the titre was 1/480 for the Asian ariety and less than 1/4 for the Scandinavian, Eire, and Dutch trains on Nov 20

Progress —Shortly after admission her temperature rose to 04 6°F, the respiration-rate increased to 44 a minute, and her condition became critical She was treated with parenteral cortisone (50 mg six-hourly) and penicillin (1 million units six-hourly) Within four hours some clinical improvement was apparent Next day her pupils reacted sluggishly to light but there was otherwise no change in her condition Her attitude was one of decerebrate rigidity, with the upper limbs medially rotated at the shoulder joints, extended at the elbows and hyperpronated, the legs were held in extension with the feet plantar-flexed On Nov 23 she began to respond to painful stimuli, and to exhibit alternating phases of rigidity and flaccidity She remained pyrexial but the respiration-rate was less rapid On Nov 25, after six days in coma, she recovered consciousness rapidly and was able to recognise her parents She was then noted to have a foot-drop on the left, with complete paralysis of the extensors and peronei, and an area of sensory impairment to pin-prick over the dorsum of the foot This was thought to be due to compression of the lateral popliteal nerve Otherwise her recovery was uneventful When seen recently, however, she complained that writing was difficult and her script had changed in character



ig 2—Case 2: electroencephalogram, Nov 21 Electrode positions as in fig 1

The Family —The mother, father, and 2 children other than cases 1 and 2 all had febrile illnesses diagnosed as Asian influenza Complement-fixation tests were done on three who were not admitted The results were

	Date	*Complement-fixation (influenza A)*	*Hæmagglutination inhibitions*			
			(Asian)	(Scan-	(Eire)	(Dutch)
Father	Nov 25	1/32	1/64	<1/16	<1/8	<1/8
	Dec 5	1/16	1/64	<1/16	<1/8	<1/8
Mother	Nov 25	1/128	1/64	<1/8	<1/16	<1/8
Daughter	Nov 27	1/128	1/128	<1/32	<1/16	<1/4

This daughter had an episode of drowsiness and headache four or five days after the febrile illness, but recovered without treatment

These results, and those of cases 1 and 2, indicate recent infection with influenza A (Asian)

Case 3 —A woman, aged 32, was admitted to the Cardiff Royal Infirmary on Nov 26, 1957 On Oct 26 she had a short illness of three days, with aching limbs, coryza, and slight cough This was thought to be influenza On Nov 1 blurring of vision, diplopia, and occasional vomiting developed Three days later she was admitted to a local hospital, where she was found to have a loss of vertical conjugate gaze and blurring of the disc edges, and the right knee and ankle jerks were more brisk than those on the left At lumbar puncture, the fluid was clear and colourless and under a pressure of 160 mm H_2O It contained no cells, and the protein content was 30 mg per 100 ml

She was transferred to the Cardiff Royal Infirmary on Nov 26, 1957, for further investigation, but by now felt perfectly well She was alert The pupils were dilated, the right more than the left, and the reaction to light was very sluggish on both sides The pupil response to convergence was impaired, and there was limitation of conjugate upward gaze The rest of the cranial nerves were normal There were no abnormal neurological signs in the upper or lower limbs, and no other abnormal physical signs were demonstrated

Investigations —Cerebrospinal fluid (C S F) under normal pressure cells 5 per c mm , protein 37 mg per 100 ml , chloride 127 mEq per litre Blood and C S F Wasserman and Kahn tests negative Blood-count normal An electroencephalogram on Nov 27 was within normal limits

Complement-fixing antibodies for influenza A were present at a titre of 1/64 (Nov 27) and 1/64 (Dec 5) By hæmagglutination inhibition the titre was 1/128 for the Asian variety and less than 1/16 for the Scandinavian, Eire, and Dutch strains, indicating a recent infection with influenza A (Asian)

Progress —While she was in hospital the diplopia cleared up completely A lumbar air encephalogram failed to reveal any abnormality She was discharged home on Dec 9, 1957

Case 4 —A girl, aged 6 years, was taken ill on Oct 23, 1957, with headache and fever Next day she felt better but was thought to have a cold. On Oct 26 she was listless and reluctant to play She was, however, well enough to travel to Cardiff next day During the journey she began to vomit and this persisted, with pain in the back of the neck, until she was admitted to a local hospital on Oct. 30 Here she was found to be drowsy but easily rousable, cooperative, and normally oriented Temperature 100 2°F, pulse-rate 110, respiration-rate 26 a minute There was a slight increase in tone and reflexes in all four limbs The plantar responses were equivocal Signs of meningeal irritation were present Lumbar puncture produced a fluid containing 80 lymphocytes per c.mm and an increased amount of globulin

Next day she was more drowsy, the tone and reflexes in the right arm and leg were exaggerated, and the right plantar response was extensor She was transferred to the Cardiff Royal Infirmary on Nov 1 She was very drowsy, but could be roused by painful stimuli Speech was limited to the word "yes", and she did not seem to understand simple instructions Neck rigidity was present, but Kernig's sign was negative Temperature, pulse-rate, and respiration-rate were normal No abnormality was demonstrated in the cranial nerves The limbs were hypotonic. There was slight weakness of the right arm and leg, the tendon reflexes on the right were slightly more brisk than those on the left The right plantar response was extensor The abdominal reflexes were not altered. No other abnormal neurological signs were detected, and the other systems were normal

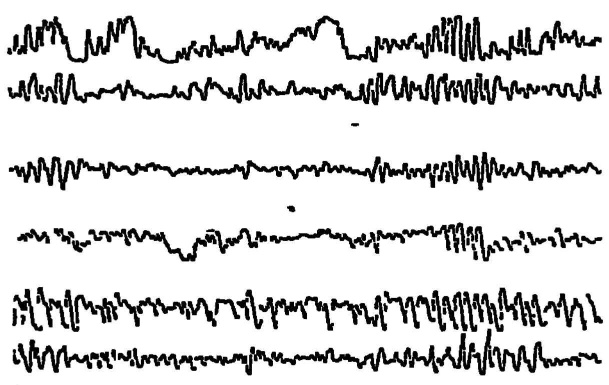


Fig 3—Case 4 electroencephalogram, Oct. 24 Electrode positions as in fig 1

Investigations —Shortly after admission the lumbar puncture was repeated pressure 55 mm H_2O, 68 lymphocytes per c.mm , protein 54 mg per 100 ml

Blood-count normal Radiographs of skull and chest normal

The electroencephalogram on the day after admission showed intermittent runs of high-voltage smooth delta waves at about 3 cycles a second in all leads A wide range of moderately high-voltage theta waves also occurred There was no subdelta or focal activity (fig 3) Complement-fixation tests gave the following titres

Date	*Complement fixation*			
	Influenza A	*Influenza C*	*Mumps*	
			S	*V*
Nov 1	1/64	1/64	1/8	1/64
Nov 4	1/64	1/64	1/8	1/64
Nov 18	1/32	1/64	1/8	1/64
Nov 27	1/64	1/32	1/8	1/32

By hæmagglutination inhibition the titre was 1/32 for the Asian variety on 3 occasions and 1/16 on Nov 18 It was less than 1/8 for the Scandinavian, Eire, and Dutch strains These figures are consistent with fairly recent infection by influenza A (Asian) virus It is likely that the febrile illness was Asian influenza, but influenza C and mumps cannot be excluded

Lumbar punctures were performed daily for four days and then at increasing intervals The cell-count rose to 1300 per c.mm on the third day after admission and then dropped steadily to 5 per c.mm on the eighteenth day At the height of the pleocytosis there was a preponderance of polymorphs, but thereafter the proportion of lymphocytes steadily increased from 60% to 90% of the total cell-count On Nov 28 the cell-count was normal The protein content varied between 40 and 80 mg per 100 ml and the sugar between 50 and 75 mg per 100 ml , and the chloride remained at about 130 mEq per litre

Progress —A provisional diagnosis of meningitis was made and she was treated with penicillin The diagnosis, however, was revised to one of encephalitis in view of the cerebrospinal-fluid findings By Nov 5 she was greatly improved and mentally alert and cooperative Speech was normal except for a nasal quality, which her parents said was normal No abnormal neurological signs could be found except for slight neck rigidity She was discharged from hospital on Nov 28 The electroencephalogram on that day showed a very great improvement

Discussion

In all these patients neurological involvement followed four or five days after the onset of a febrile illness That this febrile illness was Asian influenza appears to have been established by the results of the complement-fixation tests in 3 cases The high infectivity of the disease is shown by its spread in the family of the first 2 cases, for the other 4 members of this family had febrile illnesses, and blood from 3 showed evidence of recent infection with influenza A (Asian) Blood was not obtained from the 4th member The daughter whose blood was examined also had involvement of the nervous system following her attack of influenza She complained of severe headache and became drowsy, but recovery was uneventful Case 4 had an illness very like lymphocytic choriomeningitis, and was the only one in whom a cell response developed in the cerebrospinal fluid The illness followed what was thought to be Asian influenza, and although the results of the complement-fixation tests do not altogether exclude influenza C and mumps, we believe that the neurological disorder in this case, as in the others, followed Asian influenza.

3 of the patients (cases 1, 2, and 4) were very ill and caused some anxiety, but when recovery began it was rapid and apparently complete In cases 1 and 2 the electroencephalogram, although grossly abnormal at the height of the illness, soon reverted to normal It has since been reported that the handwriting of case 2 has deteriorated, and this is probably evidence that recovery has not been as complete as was at first thought

Summary

In 4 patients severe disorders of the nervous system followed a short febrile illness 3 of the patients had encephalitis and 1 had an illness resembling lymphocytic choriomeningitis In all of them complement-fixation tests showed evidence of a recent infection with influenza A (Asian), but in one the antibody titres for influenza C and mumps were also raised

We wish to thank Dr Idris G Jones and Mr Charles Langmaid, under whom the patients were admitted, and Dr J D Spillane for helpful criticism We are also indebted to Dr A D Evans, of the Public Health Laboratory Service, who carried out and advised us about the complement-fixation tests, and to Mr R. Marshall for the photographs

REFERENCES

Compton Smith, R. N (1958) *Lancet*, i, p 217
Dubowitz, V (1958) *ibid* p 140
Holmes, J M (1947) *Brit med J* i, 218
Jennings, G H. (1952) *ibid* i, 123
Leigh, A. D (1946) *ibid* ii, 936
McGill R. J , Goodbody, R. A. (1958) *Lancet*, i, 320

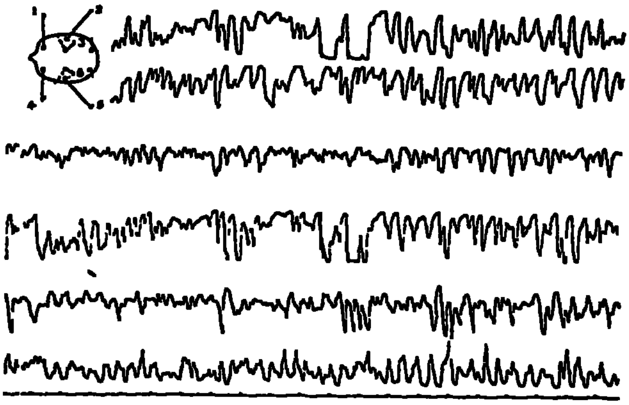


Fig 1—Case 1 electroencephalogram, Nov 21

had been taken ill at the same time as her brother and her illness followed the same course She became drowsy on Nov 18 and next morning was semicomatose She was admitted to a local hospital in coma and was transferred to the Cardiff Royal Infirmary next day

She was in deep coma There were no involuntary movements Temperature 101 6°F, pulse-rate 100, respiration-rate 35 a minute The pupils were dilated and fixed to light The fundi were normal The limbs were flaccid with symmetrically diminished tendon reflexes Both plantar responses were extensor There was no response to painful stimuli No abnormal signs were detected in the cardiovascular or respiratory systems

Investigations—Lumbar puncture on the day of admission produced a clear colourless fluid under a pressure of 90 mm H_2O cells < 5 per c mm , protein 39 mg per 100 ml , chloride 124 mEq per litre, sugar 99 mg per 100 ml

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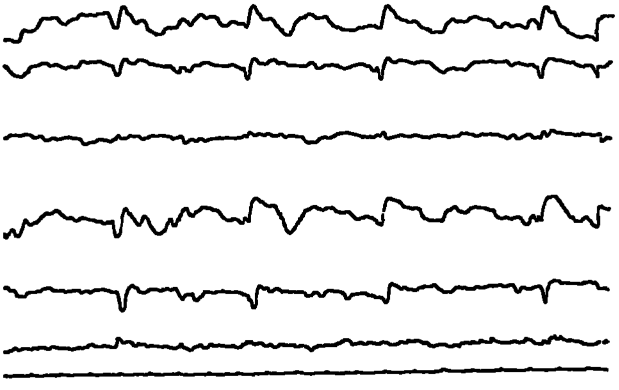

Fig 2—Case 2 electroencephalogram, Nov 21 Electrode positions as in fig 1

The Family—The mother, father, and 2 children other than cases 1 and 2 all had febrile illnesses diagnosed as Asian influenza Complement-fixation tests were done on three who were not admitted The results were

	Date	*Complement-fixation (influenza A)*	*Hæmagglutination inhibitions* (Asian)	(Scan-	(Eire)	(Dutch)
Father	Nov 25	1/32	1/64	<1/16	<1/8	<1/8
	Dec 5	1/16	1/64	<1/16	<1/8	<1/8
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These results, and those of cases 1 and 2, indicate recent infection with influenza A (Asian)

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Case 4—A girl, aged 6 years, was taken ill on Oct 23, 1957, with headache and fever Next day she felt better but was thought to have a cold On Oct 26 she was listless and reluctant to play She was, however, well enough to travel to Cardiff next day During the journey she began to vomit and this persisted, with pain in the back of the neck, until she was admitted to a local hospital on Oct. 30 Here she was found to be drowsy but easily rousable, cooperative, and normally oriented Temperature 100·2°F, pulse-rate 110, respiration-rate 26 a minute There was a slight increase in tone and reflexes in all four limbs The plantar responses were equivocal. Signs of meningeal irritation were present Lumbar puncture produced a fluid containing 80 lymphocytes per c.mm. and an increased amount of globulin.

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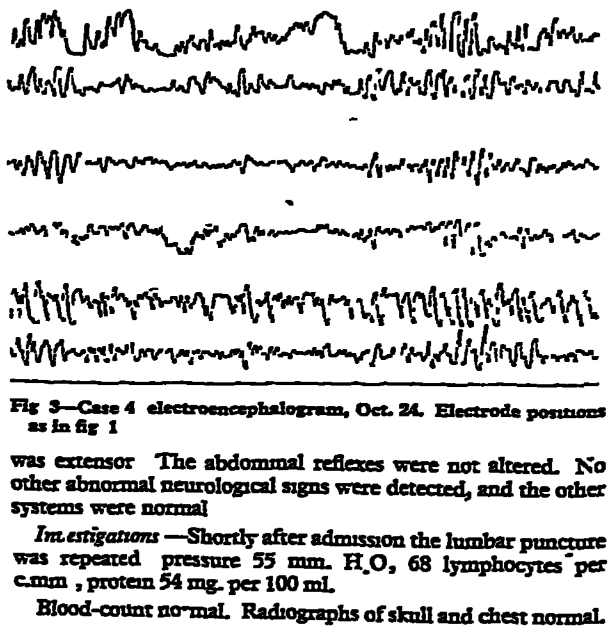

Fig 3—Case 4 electroencephalogram, Oct. 24. Electrode positions as in fig 1

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Blood-count normal. Radiographs of skull and chest normal.

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In 4 patients severe disorders of the nervous system followed a short febrile illness 3 of the patients had encephalitis and 1 had an illness resembling lymphocytic choriomeningitis In all of them complement-fixation tests showed evidence of a recent infection with influenza A (Asian), but in one the antibody titres for influenza C and mumps were also raised.

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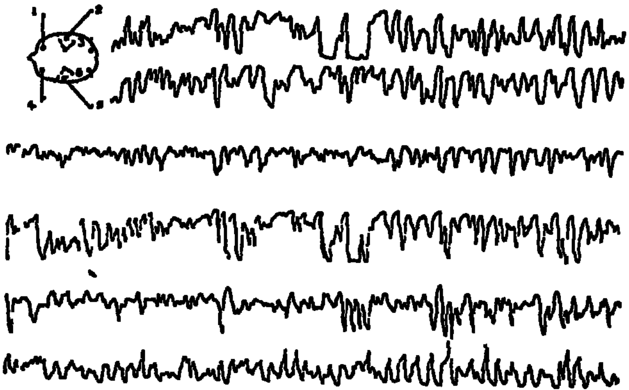

Fig 1—Case 1 electroencephalogram, Nov 21

had been taken ill at the same time as her brother and her illness followed the same course She became drowsy on Nov 18 and next morning was semicomatose She was admitted to a local hospital in coma and was transferred to the Cardiff Royal Infirmary next day

She was in deep coma There were no involuntary movements Temperature 101 6°F, pulse-rate 100, respiration-rate 35 a minute The pupils were dilated and fixed to light The fundi were normal The limbs were flaccid with symmetrically diminished tendon reflexes Both plantar responses were extensor There was no response to painful stimuli No abnormal signs were detected in the cardiovascular or respiratory systems

Investigations —Lumbar puncture on the day of admission produced a clear colourless fluid under a pressure of 90 mm H_2O cells < 5 per c mm , protein 39 mg per 100 ml , chloride 124 mEq per litre, sugar 99 mg per 100 ml

Hb 15 5 g per 100 ml , leucocyte-count 11,800 per c mm (91% polymorphs) Platelet-count on Nov 25, 65,000 per c mm , Dec 5, normal A radiograph of the chest revealed no abnormality

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Progress —Shortly after admission her temperature rose to 104 6°F, the respiration-rate increased to 44 a minute, and her condition became critical She was treated with parenteral cortisone (50 mg six-hourly) and penicillin (1 million units six-hourly) Within four hours some clinical improvement was apparent Next day her pupils reacted sluggishly to light but there was otherwise no change in her condition Her attitude was one of decerebrate rigidity, with the upper limbs medially rotated at the shoulder joints, extended at the elbows and hyperpronated, the legs were held in extension with the feet plantar-flexed On Nov 23 she began to respond to painful stimuli, and to exhibit alternating phases of rigidity and flaccidity She remained pyrexial but the respiration-rate was less rapid On Nov 25, after six days in coma, she recovered consciousness rapidly and was able to recognise her parents She was then noted to have a foot-drop on the left, with complete paralysis of the extensors and peronei, and an area of sensory impairment to pin-prick over the dorsum of the foot This was thought to be due to compression of the lateral popliteal nerve Otherwise her recovery was uneventful When seen recently, however, she complained that writing was difficult and her script had changed in character

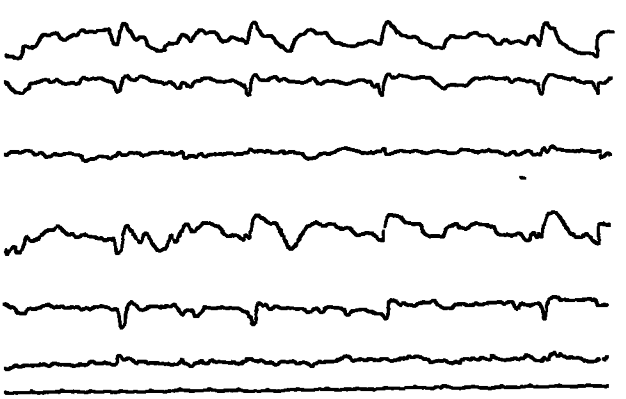

Fig 2—Case 2 electroencephalogram, Nov 21 Electrode positions as in fig 1

The Family —The mother, father, and 2 children other than cases 1 and 2 all had febrile illnesses diagnosed as Asian influenza Complement-fixation tests were done on three who were not admitted The results were:

	Date	*Complement-fixation (influenza A)*	*Hæmagglutination inhibitions* (Asian)	(Scan-	(Eire)	(Dutch)
Father	Nov 25	1/32	1/64	<1/16	<1/8	<1/8
	Dec 5	1/16	1/64	<1/16	<1/8	<1/8
Mother	Nov 25	1/128	1/64	<1/8	<1/16	<1/8
Daughter	Nov 27	1/128	1/128	<1/32	<1/16	<1/4

This daughter had an episode of drowsiness and headache four or five days after the febrile illness, but recovered without treatment

These results, and those of cases 1 and 2, indicate recent infection with influenza A (Asian)

Case 3 —A woman, aged 32, was admitted to the Cardiff Royal Infirmary on Nov 26, 1957 On Oct 26 she had a short illness of three days, with aching limbs, coryza, and slight cough This was thought to be influenza On Nov 1 blurring of vision, diplopia, and occasional vomiting developed Three days later she was admitted to a local hospital, where she was found to have a loss of vertical conjugate gaze and blurring of the disc edges, and the right knee and ankle jerks were more brisk than those on the left At lumbar puncture, the fluid was clear and colourless and under a pressure of 160 mm H_2O It contained no cells, and the protein content was 30 mg per 100 ml

She was transferred to the Cardiff Royal Infirmary on Nov 26, 1957, for further investigation, but by now felt perfectly well She was alert The pupils were dilated, the right more than the left, and the reaction to light was very sluggish on both sides The pupil response to convergence was impaired, and there was limitation of conjugate upward gaze The rest of the cranial nerves were normal There were no abnormal neurological signs in the upper or lower limbs, and no other abnormal physical signs were demonstrated

Investigations —Cerebrospinal fluid (C S F) under normal pressure cells 5 per c mm , protein 37 mg per 100 ml , chloride 127 mEq per litre Blood and C S F Wasserman and Kahn tests negative Blood-count normal An electroencephalogram on Nov 27 was within normal limits

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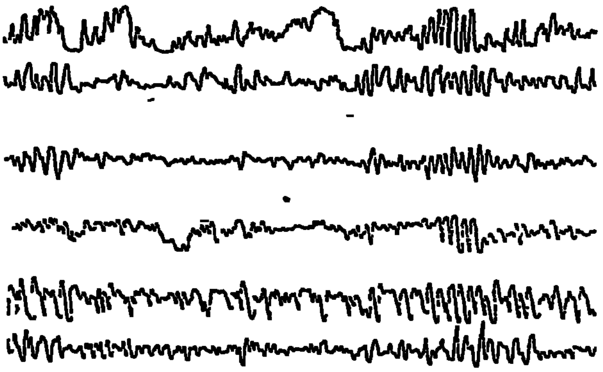

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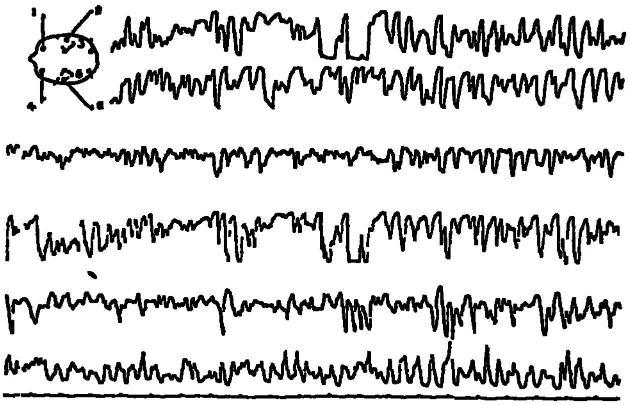

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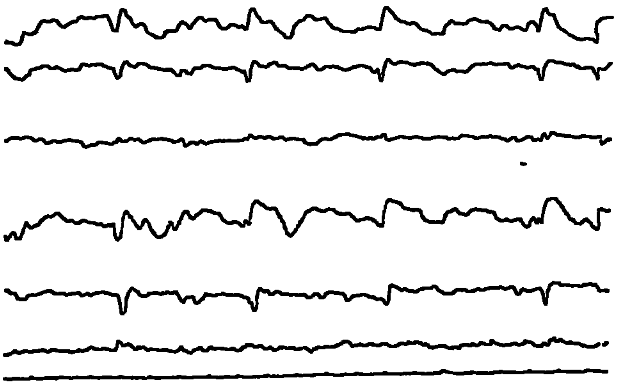

Fig 2—Case 2 electroencephalogram, Nov 21 Electrode positions as in fig 1

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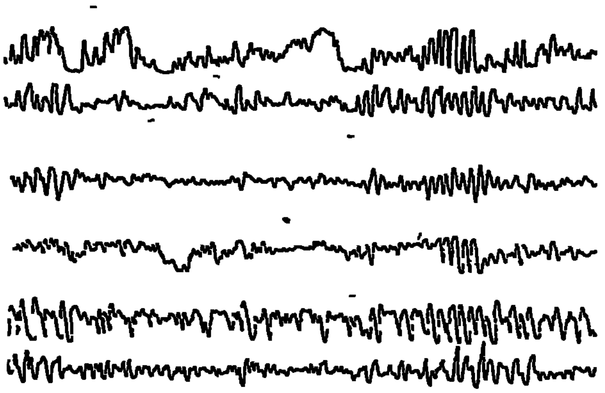

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Holmes, J. M. (1947) *Brit. med. J.* i, 218.
Jennings, G. H. (1952) *ibid.* i, 123.
Leigh, A. D. (1946) *ibid.* ii, 936.
McGill, R. J., Goodbody, R. A. (1958) *Lancet*, i, 320.

ACUTE PSYCHOSES DUE TO ENCEPHALITIS FOLLOWING ASIAN INFLUENZA

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THERE have been three great influenza pandemics in e past seventy years, and after each of them various omplications have been reported pneumonia and myoarditis, first described by Leichtenstern in 1896 (Lyon 956), encephalitis (Leichtenstern 1890, Pfuhl 1892), and sychoses (Rorie 1901) In the influenza epidemic in erusalem in 1957 we encountered acute psychotic anifestations in three children

Case-reports

Case 1 —A boy, aged 15, was admitted on Sept 25, 1957, an acute state of confusion, anxiety, and restlessness He ied and clung to his mother, claiming that she wanted to ave him His parents related that, a week before, the boy had omplained of severe frontal headaches In spite of this he ontinued to attend school until two days before admission, hen he suddenly left school before the end of lessons, apparntly owing to an argument with his teacher He was very stless when he came home and begged his mother to protect m from his teacher and not to abandon him On the eve of s admission he suddenly tried to strangle his mother

On examination no general or neurological abnormalities ere found The boy was in a state of great tension and kept s eyes closed all the time, claiming that his mother had rbidden him to open them He begged continuously for his other so that he might suck milk from her, expressing that me wish to every nurse who entered his room He masrbated for hours and wet his bed He refused food of any nd No contact could be established with him

Treatment and progress —Because of his extreme restlessness e was kept under constant sedative and tranquillising treatent During the first five days he had slight pyrexia, which se only once to 103 1°F On the second day after admission rced grasping of his left hand was noticed The first impreson was that the boy had acute hysteria probably connected ith the argument at school with his teacher The forced rasping which appeared later seemed to indicate an organic asis to his illness Further support for this assumption was rovided by electroencephalography the record was grossly bnormal, with generalised slow activity of the delta range, ith high amplitude mainly localised in the posterior regions f the brain (fig 1) Repeated electroencephalography during the next eight days, showed similar diffuse abnormal patterns Other investigations, including radiography of his skull and chest and chemical analysis of his blood and cerebrospinal fluid (C S F) were normal On the sixth day in hospital the boy grew calmer His whole appearance changed, he became quiet, shy, and well behaved He dressed neatly and ate normally His orientation in time and place was good, but he remembered nothing of his illness A fortnight after the onset he was back at school, a composed pleasant boy without any abnormal behaviour

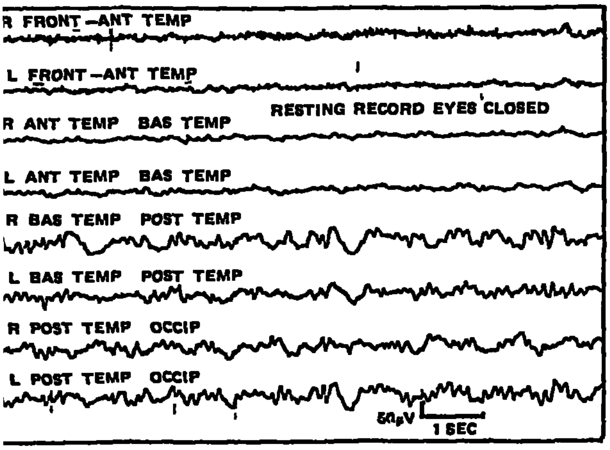

Fig 1—Case 1 resting electroencephalogram

Follow-up —Repeated electroencephalography in the three months following his discharge showed a clear improvement, although the records were still moderately abnormal, with diffuse theta activity (fig 2) Only sporadic cases of Asian influenza had been reported in Jerusalem at the time of the boy's illness, so we did not relate this acute psychotic reaction to influenza A later epidemiological investigation revealed, however, that all six members of the boy's family had had Asian influenza after he had been admitted to hospital Moreover influenza had already been reported among his neighbours three days before the onset of his illness In view of this a sample of his blood was sent to be tested for hæmagglutinin inhibition of influenza virus A/Singapore/1/57, and a titre of 1 382 was found, proving that the boy had had Asian influenza before his acute psychosis

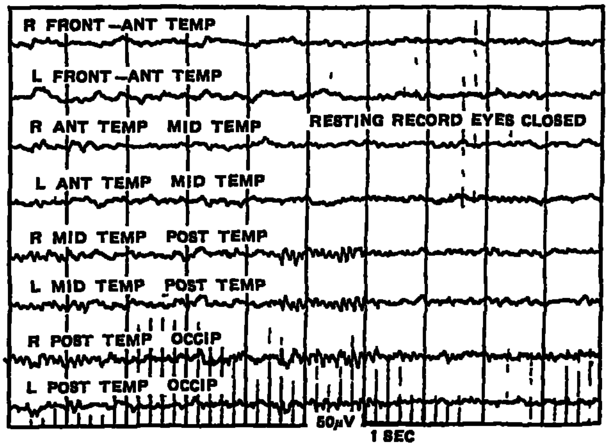

Fig 2—Case 1 resting electroencephalogram three months after discharge

Case 2 —A girl, aged 11½ years, had been ill for ten days In the family all four children as well as the mother had had a febrile disease which had been diagnosed as Asian influenza After recovery the girl attended school again, but after a week she returned from school complaining of headaches She lay in bed for twenty-four hours in almost complete apathy Then suddenly she became very restless, got out of bed, ran about the house, and went to neighbours, telling them that her father had killed her mother, and that she was left alone The girl complained that she was being followed all the time by a woman who was trying to catch her She presented a picture of acute anxiety and was brought to the hospital in that condition

On admission physical and neurological examination and lumbar puncture did not reveal any abnormalities The blood-count was normal, and the erythrocyte-sedimentation rate (E S R) was 50 mm in the first hour (Westergreen) Electrocardiography gave a normal tracing Radiography of the skull was normal, but radiography of the chest showed a slight shadowing in the inner part of the lower left lung and, to a lesser degree, on the right side too On the basis of this finding viral pneumonia was diagnosed The titre for influenza virus A/Singapore/1 57 was 1 384 Electroencephalography gave a very abnormal record with generalised slow theta and delta

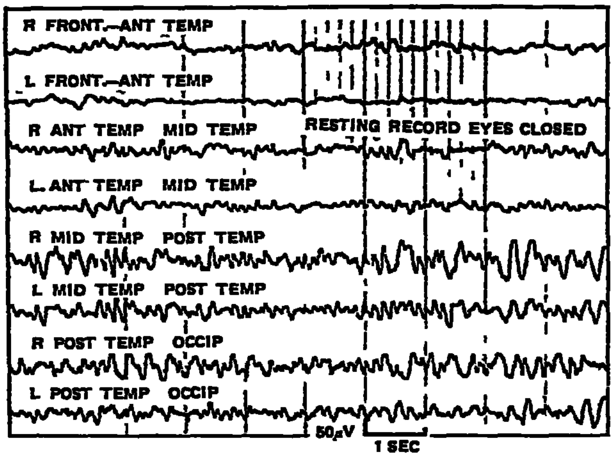

Fig 3—Case 2 resting electroencephalogram

activity (fig 3). During photic stimulation bursts of slow waves and spikes appeared, especially on closure of the eyes (fig 4). Contact was most difficult to establish with the girl. She remained silent most of the time. Occasionally she would wander about the department looking absolutely lost. At times she would cry and yell for hours for no apparent reason. After four days she gradually calmed down and recognised people, especially her family. She remembered nothing of her illness. A radiograph of her chest before her discharge was normal. After a fortnight she returned to normal life, feeling quite well.

Follow-up.—Repeated electroencephalography after her discharge showed a gradual improvement, although the tracings were still abnormal, with diffuse theta activity and sporadic spiky activity during photic stimulation.

Case 3.—A boy, aged 9½ years, brother of case 2, was admitted on Nov. 20, 1957. Three weeks earlier he had been ill, together with other members of his family. During the last two days of his illness he was very restless, got out of bed, moved around aimlessly, and mumbled only incomprehensible words. Although he was known to be mildly retarded, attending a special school for such children, his mother found his behaviour unusually strange and abnormal during his illness. These signs disappeared gradually in two or three days. He became quiet again, went back to school, and for a week was well. Ten days after his recovery he suddenly returned from school before the end of lessons, complaining of severe headache and general malaise. At that time his orientation in time and place was still good. He was put to bed. During the next two days he again became restless, cried, and shouted. He complained that somebody was trying to catch and beat him. He was in an extreme state of tension and anxiety and apparently had fears and hallucinations. In this condition he was admitted to hospital.

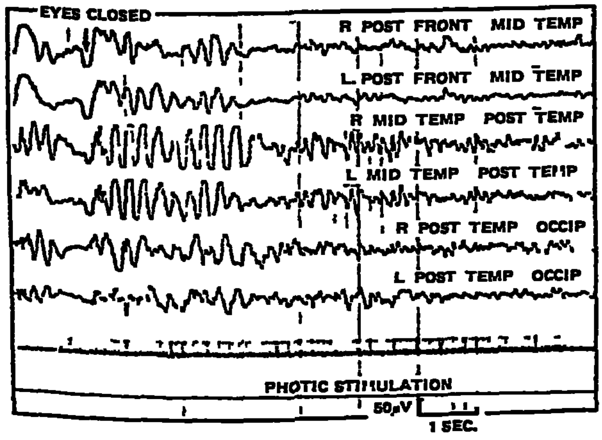

Fig 4—Case 2 electroencephalogram during photic stimulation

On admission physical and neurological examination, radiography of his skull and chest, and routine laboratory examinations revealed no abnormal findings. Culture of his C.S.F. for influenza virus was negative. His blood titre for influenza virus was 1 192. Electroencephalography gave a diffusely disturbed record with increased theta and delta activity, mainly in the posterior regions of the brain (fig 5). This confirmed the tentative diagnosis of an organic psychosis in connection with the influenza. Electrocardiography gave an abnormal record with S-T depression in L2 and L3 with T waves of low voltage. On the basis of this finding postinfluenzal myocarditis was also considered.

Progress.—Within ten days the boy calmed down. His whole expression changed, becoming serene, with no signs of fright or anxiety any longer. He started to become oriented in time and place but could not recall what had happened to him, or how he had come to be in hospital. Repeated electroencephalography still gave diffusely abnormal tracings. Electrocardiography seven days later was again abnormal, showing notched T waves in V_3 and V_4. Electrocardiography a week later still was within normal limits. The boy was discharged after a fortnight. He went back to school, but after ten days he apparently had a relapse of the psychotic reaction and was readmitted in a state similar to that described above, characterised by restlessness and anxiety.

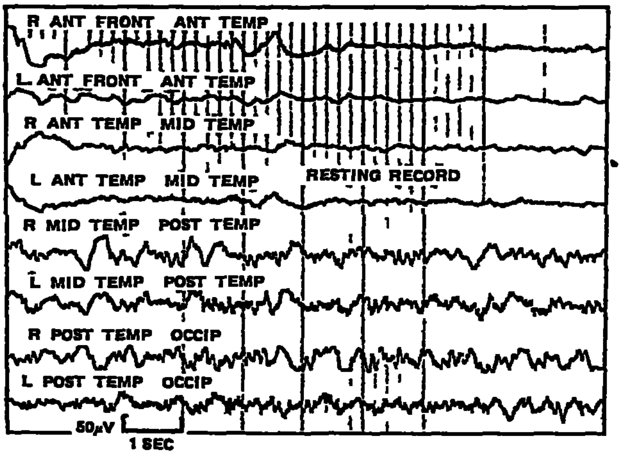

Fig 5—Case 3 resting electroencephalogram

On readmission physical examination revealed wet rales over both his lungs. A grade-II systolic murmur was heard over the base of his heart. His pulse-rate was 120, blood-pressure 120,80 mm. Hg, and liver slightly enlarged. Neurological examination revealed no abnormalities. The E.S.R. was 19 mm. in the first hour (Westergreen). The titre of influenza virus A/Singapore/1/57 hæmagglutinin inhibition in the blood was 1 383—much higher than during his first stay in hospital. Radiography of his chest showed an enlarged hilum of the left lung and patchy shadows at the base of both lungs. Electroencephalography gave a most abnormal record, worse than on the first stay in hospital, showing much theta and delta activity. Electrocardiography showed inverted T waves in V_3 and V_4 and a prominent R wave in aVR, this being a significant change in comparison with the previous electrocardiograms, indicating right ventricular strain and myocardial damage.

Treatment was started immediately with antibiotics, digitalin, and sedatives. At the end of a week the boy recovered from the acute psychotic state and became calm and well oriented again.

Follow-up electrocardiography, although showing an improvement, was still abnormal, with notched T waves in V_2 and V_3

Discussion

All three patients developed psychotic manifestations from two to ten days after the onset of Asian influenza These manifestations were almost identical in all the cases, including signs of acute anxiety, confusion, extreme restlessness, and ideas of persecution The acute psychotic symptoms receded within the relatively short period of from six to eight days, leaving the patients with complete amnesia about what had happened to them during the acute stage of the illness These three patients were children aged less than 16 Another feature common to all the cases was the diffusely abnormal electroencephalograms which remained abnormal long after the clinical recovery of the patients

The appearance of acute psychotic states after influenza has been a well-established fact ever since the great influenza pandemic of 1899–1900 (Dillon 1909, Rouge 1909, Graves 1928, Bartstra and Pesman 1950) The manifestations described were manifold and included depressions, manic conditions, amentias, acute delirious states, hysterical reactions, ideas of persecution, and hallucinations (Rorie 1901, Jelliffe 1918) At the beginning of the century some workers argued for and against a direct connection between such psychotic manifestations and influenza Klemm (1901) rejected the idea of "specific" influenzal psychoses, claiming that, in some patients at least, the psychosis was latent and only activated by the influenza Other workers suggested bacteriological examinations as a means of correlating the onset of the psychosis with the influenza Thus Neumann (1914) suggested that the influenza microbe (*Hæmophilus influenzæ*) should be isolated from the C S F by culture on pigeon's blood-agar In case 3 the striking rise in titre of the influenza virus hæmagglutinin inhibition found during the boy's second psychotic outbreak provided immunological proof of a correlation between the activity of the influenza virus and the psychosis Another bridge between these psychotic manifestations and the Asian influenza in the present cases was provided by electroencephalography, which revealed an abnormal pattern The diffuse abnormal electrical activity of the brain in these patients supported the diagnosis of postinfluenzal encephalitis, whose only clinical manifestation was the acute psychosis

Summary

Acute psychosis came on after Asian influenza in three children

In all three cases diffuse abnormal electrical activity of the brain was recorded

The acute psychosis was apparently the only clinical manifestation of encephalitis

Clinical remission occurred in a relatively short time, appearing much earlier than normal electroencephalograms

I wish to thank Prof L Halpern for his most helpful criticism and advice

REFERENCES

Bartstra H K G, Pesman, J (1950) *Folia psychiat neerl* 53, 771
Dillon, H V M (1909) *Lancet*, ii 1498
Graves, T C (1928) *J Neurol Psychopath* 9 97
Jelliffe, S F (1918) *N Y med J* 108 725 755 807
Klemm, F (1901) cited in *Neurol Zbl* 20 966
Leichtenstern, M H (1890) *Dtsch med Wschr* 16, 212 389 485
Lyon E (1956) Virus Diseases and the Cardiovascular System New York and London
Neumann, K T (1914) cited in *Neurol Centralblatt*, 35, 316
Pfuhl A (1892) *Berl klin Wschr* 29 979, 1009
Rorie, G A (1901) *J ment Sci* 47, 317

PSYCHOSIS FOLLOWING ASIAN INFLUENZA IN BARBADOS

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"Asian" influenza* was first reported in Barbados on Sept 14, 1957, and in the five weeks from Sept 25 to Oct 31 no fewer than nineteen cases of psychosis definitely attributable to it were admitted to the Mental Hospital Fourteen gave a clear history of influenza preceding their mental breakdown, and some of these were admitted while still pyrexial

Fourteen of the patients were women and five were men, their ages ranged from 15 to 67 (average 28, median 24) Most of them were restless, noisy, resistive, and disoriented, and some were untidy and faulty in habits Seven had hallucinations, and four of these were rational and well-behaved in contrast to the general excitement and confusion shown by the rest of the group These seven all complained of a strange unpleasant smell but could not describe it clearly

> "Unlike anything I know"
> "Unpleasant smell which I can't describe"
> "Like a dead smell"

These patients had no such difficulty in describing their visual and auditory hallucinations

Illustrative Case-reports

Case 10 A woman, aged 26, *was admitted from the* General Hospital with a temperature of 100 6° She was restless, resistive, noisy, and obscenely abusive, and she refused to wear any clothes She improved rapidly on electroconvulsion therapy (E C T) and was discharged on trial after 21 days

Case 2—A girl, aged 16, was restless, noisy, talkative and abusive She gave a hisory of having had influenza recently She was given E C T but made only slow progress, gradually becoming less hyperactive and abusive She was discharged on trial after 59 days

Case 18—A man, aged 36, was quiet, well behaved, well oriented, and rational in speech, but had striking aural, visual, and olfactory hallucinations He saw large and small spirits, *with no clothes on and experienced a sweet smell which he* was unable to describe and was unlike anything he knew His blood Kahn test was positive but his cerebrospinal fluid Kahn and colloidal-gold tests were negative

He improved rapidly on E C T and was discharged on trial after 24 days

Case 17—A man, aged 25, was rational and well oriented, but had aural, visual, and olfactory hallucinations He saw animals at the windows, and complained of a filthy smell, but appeared to realise that these phenomena were not real Two *days after admission he became violent and attacked the* nurses, under the delusion that he was a gorilla His mother and father had both been discharged from the mental hospital earlier in the year, the mother with a hallucinatory syndrome, and the father with an alcoholic confusional psychosis He recovered rapidly with E C T and was discharged on trial after 26 days

The toxic psychosis, whether primarily confusional or hallucinatory, cleared up rapidly Four patients had no specific treatment, and fifteen were given a short course of electro-convulsion therapy, two of the fifteen had insulin as well Within 17 weeks all had been discharged, with an average hospital stay of 38 days

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*Though the diagnosis was not confirmed by virological methods, the outbreak coincided with others, in neighbouring areas, which were thus confirmed Epidemiologically the outbreak—explosive and widespread—*was not at all like the influenza to which we have been accustomed in Barbados*

Comment

It is impossible to give the incidence of toxic psychosis following Asian influenza in Barbados, because the epidemic, though widespread, was not severe, and many of those affected (among the population of about 230,000) did not consult their doctors Moreover, it appears that some patients with mental symptoms following influenza were successfully treated at home by the family doctor The presence of psychosis could not be correlated with the severity of the febrile attack, most of the affected patients were incapable of giving any history about their confusional state, and their relatives were of little help In the two cases where the patient had previously been in the Mental Hospital the influenzal attack may be regarded as merely precipitating a relapse

Summary

A toxic psychosis was seen in 19 patients in Barbados shortly after (or towards the end of) an attack of Asian influenza Most were young adults

15 patients had electroconvulsion therapy and 2 insulin as well 4 had no treatment All recovered rapidly

7 patients presented an unusual hallucinatory syndrome, in which bizarre smells were often experienced

I wish to thank Dr R A Webb for his assistance in compiling this report, and Dr M A Byer, director of medical services, for permission to publish it

HEPARINISED BLOOD FOR EXCHANGE TRANSFUSION

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In blood-transfusion the use of citrate as the anticoagulant has become almost traditional For most purposes it is entirely satisfactory, and it has the advantage that blood treated with suitable citrate-dextrose mixtures can be kept long enough to be held in stock against an emergency However, the work of Firt and Hejhal (1957), on the toxicity of citrated blood given in large rapid transfusions raises the question of whether it is ideal for exchange transfusions in the newborn The sudden collapse seen occasionally during exchange transfusion could be due to citrate intoxication

In other respects citrated blood may not be ideal for exchange transfusion The addition of acid-citrate-dextrose mixtures lowers the hæmoglobin content of the donor blood by simple dilution, and can lead to expansion of the red cell by as much as 20% (Mollison 1951) If the cells shrink to normal size after they are transfused, the patient receives, in effect, a transfusion of blood with a low packed-cell volume Neither of these effects is desired

The removal of part of the supernatant citrated plasma after sedimentation of the red cells would cancel both the dilution of the donor blood and the expansion of the red cells, and would lessen the likelihood of citrate intoxication the use of sedimented erythrocytes for exchange transfusion is recommended by Sisson et al (1958) But it is more rational to use some other anticoagulant Experience with heparinised blood is here recorded

Material and Method

In 1948–54 I had personal experience of about 70 exchange transfusions in English hospitals, using citrated blood The records are not readily available, but there were several cases of severe shock, which appeared to be due to acute heart-failure This developed towards the end of the transfusion and was common enough to make one approach exchange transfusion with some apprehension 3 babies died The same syndrome was observed in Canada in 1954–55 when citrated blood was used, though the exchanges were done slowly with 10ml aliquots, a blood-volume deficit was maintained, frequent halts were observed during the exchange, and calcium gluconate was given at each 100 ml of the exchange

In November, 1955, I began to use heparinised blood in an attempt to avoid this syndrome, and I have not used citrated blood since 21 exchange transfusions have been performed 9 babies with rhesus hæmolytic disease received 13 exchange transfusions, 5 with ABO incompatibility disease received 7, and 1 with severe "physiological" jaundice was given 1 This last, aged 12 days, was transfused through the saphenous vein at the groin, but in the remainder the umbilical vein was used

The indications for exchange transfusion, in a baby with rhesus hæmolytic disease, have been

1 A birth-weight under $5^1/_2$ lb
2 A cord-blood hæmoglobin under 15 g per 100 ml
3 A cord-blood bilirubin over 2 8 mg per 100 ml
4 A capillary-blood bilirubin of 20 mg per 100 ml or over at any time

Transfusions were also given to babies with ABO hæmolytic disease or with "physiological" jaundice in whom the bilirubin rose to 20 mg per 100 ml or above at any time In a really small baby I would have performed an exchange transfusion at a lower level of bilirubin than 20 mg, but such a case did not arise From November, 1955, to December, 1957, 30 babies were assessed and 15 were selected for treatment

Blood has been obtained from a panel of donors living in the town and has been collected by gravity into silicone-coated bottles, to which 1500 I U (1 5 ml) of heparin had just been added Care was necessary to ensure thorough mixing of the blood and heparin during withdrawal

An exchange of 80 ml per pound body-weight was considered desirable, and enough blood was taken for this 1500 I U of heparin sufficed for 450–600 ml With a large baby more than one donor has been used

While the blood was being collected, preparations were being made for the transfusion, so that the exchange could start as soon as compatibility of the blood had been established Thus the blood was in use within forty-five minutes of collection and while it was still warm

The technique of the exchange was conventional except that a three-way direct-flow syringe (Allen and Hanburys, catalogue no 16486) was used This syringe, together with an infant's (size 8 French) clear plastic œsophageal feeding-tube, greatly facilitates the procedure Before the replacement was begun, the syringe and tubes were flushed with physiological saline solution containing 100 units of heparin per ml This solution was all expelled, and no heparin was injected into the baby apart from that in the donor blood Aliquots of 10 ml were used in all exchanges, in the early cases, at the start of the replacement, 15 ml was removed and 10 ml given until there was a deficit of 25 ml Latterly this precaution has been omitted

At the end of the transfusion the catheter was removed and two or three fine nylon sutures used to close the skin over the umbilical root so that it might be kept fresh and clean in case another exchange was needed Repeat exchanges have been done with the same technique Neither antibiotics nor protamine sulphate were used

Results

In the 21 exchange transfusions with heparinised blood no difficulties arose In two cases, a few drops of blood oozed from the umbilical stump, but this ceased within an hour or two Surprisingly, there was no bleeding at the incision in the case where the saphenous vein was used

The babies stood the procedure very well and nothing resembling the shock syndrome was observed in this series

Discussion

This small series affords no proof that the absence of shock was related to the substitution of heparin for citrate, but the change was made in the hope of avoiding collapse, and this hope was realised From the work of Firt and Hejhal (1957) it certainly seems that citrated blood might precipitate cardiac failure both by direct action on the myocardium and by vasoconstriction in the pulmonary vascular bed In their experiments citrate intoxication caused a rise in venous pressure, and it is well known that such a rise may occur during exchange transfusion

Final hæmoglobin levels when heparinised blood was used were not compared with those when citrated blood was used, but it is a reasonable assumption that the final levels would be higher when the fluid transfused contained only 1 5 ml of anticoagulant solution than when it contained a much larger volume

Because it keeps poorly, and because it would be inappropriate for many patients with hæmorrhage, heparinised blood cannot be used routinely for transfusion But in exchange transfusion for hæmolytic disease of the newborn, time can nearly always be taken to obtain a donor and to match the bloods Time taken to ensure that the blood used for exchange transfusion is fresh and heparinised may be time well spent

This also is the experience of Pew (1956) in his preliminary report of a very similar technique

Summary and Conclusion

In 21 exchange transfusions in newborn babies, the use of heparin as the anticoagulant proved simple and safe Because citrate is toxic in large rapid transfusions, heparinised blood seems preferable for this purpose

REFERENCES

Firt P , Hejhal, L (1957) *Lancet*, ii, 1132
Mollison, P L *Blood Transfusion in Clinical Medicine*, pp 407–408 Oxford 1951
Sisson, T R C, Whalen, L E, Telek, A *Pediatrics* (1958) 21, 81
Pew, W L (1956) *J Pediat* 49, 570

SEROUS OTITIS AS A CAUSE OF CATARRHAL DEAFNESS IN CHILDHOOD

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CATARRHAL deafness in childhood is important and often misdiagnosed The schoolteacher may call the child backward, the parent may say that it is inattentive and naughty, and often the child does not realise that it is deaf Catarrhal deafness is not necessarily associated with earache or discharge from the ears, and it is not a very severe form of deafness in most cases Usually it has a variable course, and most children are cured either spontaneously or by the removal of adenoids and nasal infection, but in a few it becomes irreversible, persisting into adult life as a handicap which does not respond to treatment

In the present investigation 96 of 1000 children consecutively referred to an ear, nose, and throat clinic in the past three years had catarrhal deafness All the children with a perforated tympanum, whether wet or dry, were excluded from this number, and so were all the children whose deafness disappeared after politzerisation The children with catarrhal deafness were aged 4–15 years, and there were 50 boys to 46 girls

TABLE I—OPERATIONS IN RELATION TO MIDDLE-EAR FINDINGS

53 children with proved serous otitis	Fluid in			Total
	Both ears	Rt ear	Lt ear	
Tonsils and adenoids removed at operation	8		11	19
Adenoids alone removed at operation	8	4	2	14
+*Proof puncture of antra producing mucopus*				
Bilateral	10	1	1 }15	
Unilateral			3	
Adenoids removed elsewhere				
Adenoids present	6	1	3	10
Adenoids absent	3	5	2	10
+*Proof puncture of antra producing mucopus*				
Bilateral	3		1 }5	
Unilateral		1		
Thick mucus present	15	3	2 }20	53

Remaining 43 cases	Dry on stab puncture	No stab puncture	
Tonsils and adenoids removed	15	9	24
Adenoids alone removed	9	1	10
Adenoids removed elsewhere			
Adenoids present	4	1	5
Adenoids absent	3	1	4
+*Proof puncture of antra producing mucopus*			
Bilateral	3	1 }9	
Unilateral	4	1	
Total	—	—	43

Operative Findings

It is unusual to see a deaf child with a normal tympanum It was therefore decided, at operation, to attend to the tonsils and adenoids and nasal infection in accordance with the history and clinical findings and simultaneously to examine the ears for abnormal appearance or mobility of the tympanum 53 children had fluid in one or both ears, and of the remaining 43 children 31 had empty middle ears on stab puncture, and in 12 stab puncture was not done, because the drumhead appeared normal In 33 of the 53 cases of proved serious otitis the fluid was thin, and in 20 it was very tenacious thick mucus 29 children had previously been rid of their adenoids, and 15 of these still had adenoids Table I sets out the operations in relation to the findings in the middle ear

Duration and Type of Deafness

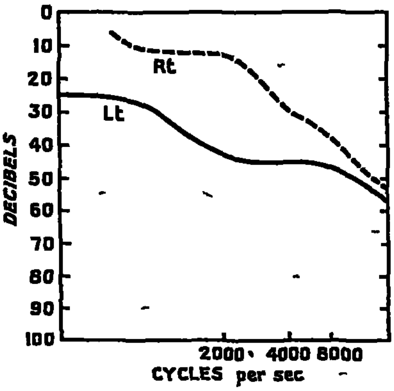
The history of these children is interesting in relation to these operative findings In 31 cases a parent could state the duration of the deafness accurately (table II)

TABLE II—DURATION OF DEAFNESS IN RELATION TO MIDDLE-EAR FINDINGS

—	Fluid present		Dry on stab puncture	No stab puncture
	Thin	Thick		
Duration of deafness (mos)	24 36 12 18 4 10 7 48 12 2 18 1 24 1 2	12 84 24 24 60 12 24 24 12 24	2 3 6	3 2 6
No of cases (% of each group total)	15 (*46%*)	10 (*50%*)	3 (*10%*)	3 (*25%*)

In 15 cases the parents were unaware of deafness at the clinic, and in the remaining 50 cases the parents usually said that deafness came on with colds 3 children were deaf after a previous adenoidectomy, 26 had a history of discharge from the ear, and 16 were said never to have had earache It is surely very significant that the parents who noticed deafness continuously and for the longest duration in most cases were those whose children had serous otitis

Audiographs were recorded in 10 of the more reliable children, and in 6 of these a loss of high tones was found



The accompanying air-conduction graph is from one of these In all the children variation in the degree of deafness was prominent

The degree of deafness was in no case severe, and in 2 children who had fluid in the middle ear only a slightly reduced response to the whispered voice was found Unless, therefore, the ear is examined very thoroughly for abnormal appearance and mobility, such cases may be easily missed

Association with Allergy

In this group of 96 children 8 were considered, by virtue of their history and examination, to be allergic Asthma, frequent sneezing, and bronchitis in infancy were regarded as important in this respect Nasal smears were not done as a routine, but in 2 cases small biopsy specimens from the inferior turbinate confirmed allergy 6 of these children had fluid on stab puncture and in 2 of these it was very thick mucus At follow-up all the children had normal hearing and a normal appearance of the tympanum, although 2 children required a second stab puncture In 3 cases the antra, when washed out, were found to be infected

Appearance of the Tympanum

No specific appearance of the drum characterised serous otitis, but its pathological condition was recognised more and more successfully with practice The mobility of the drum, determined with a Siegle's speculum, was reduced or absent in many cases, but in a few children with very thick mucus the mobility was apparently normal The commonest finding in serious otitis was a fatty yellow colouration of the tympanum, which had its normal lustre and in some cases appeared to be indrawn A slate-grey tympanum was not found in this series 3 children came to the clinic with air-bubbles in the middle ear A fluid level was never seen In 6 cases the drumhead appeared to be overmobile, and in all of these fluid was found at operation

Treatment

Most authorities agree that paracentesis of the drum should be done if fluid in the middle ear is suspected (Politzer 1869, Suehs 1952, Rawlins 1954) It is preferable to do this after inflating the middle ear to prevent damage to the mucosa over the promontory This is not always possible, because in some cases the eustachian tubes are blocked In this series a paracentesis or stab puncture was done under anæsthesia with a Trautmann's myringotomy knife in all the cases in which there was any alteration of the appearance or the mobility of the tympanum In 2 cases the tympanum was of normal appearance and mobility but previous audiographs had shown moderately severe deafness, and for this reason alone a stab puncture was done, thick mucus was found After the stab puncture characteristically a drop of straw-coloured fluid would appear Suction was applied until the middle ear was empty, after which the ear and tube were inflated with the Siegle's speculum When thick mucus was present, suction applied to the stab wound produced a tenacious thread of mucus which could often be drawn out beyond the external meatus When all the mucus was removed, the drumhead appeared baggy and overmobile, and in some children this appearance persisted In a few cases in which no fluid was produced stab puncture restored the mobility of the drum to normal after inflation with the Siegle's speculum

Several children, not in this series, have tolerated a stab puncture in the clinic, but it is important to be quite sure that fluid is present before doing this, because only then is it almost painless Some workers have suggested that two stabs be made at the same time in different parts of the tympanum This seemed to be unnecessary under anæsthesia because then suction could be used, but in adults it is useful in difficult cases No adverse effects resulted from stab puncture The wound heals in a few hours, and the scar migrates to the periphery of the tympanum, where it disappears

Results of Treatment

65 children were examined after an interval of 6–36 months after the operation 9 were still deaf Table III shows the distribution of cases

The presence of fluid in 6 of the 9 cases still deaf at follow-up was confirmed at a second operation

Character of the Fluid

The thin fluid of serous otitis is yellowish, sticky, and mucinous The thick fluid is greyish white and can be drawn out into knotty strands In 2 cases of serous otitis (not in this series) fluid was collected in sufficient quantity to be analysed I am indebted to Dr H J Gibson for the following reports

(1) Bright amber fluid, fairly clear, viscosity ++ Cells 420 per c mm, mainly degenerate tissue cells with a few lymphocytes Protein 8 5 g per 100 ml Sodium 280 mg per 100 ml = 125 m Eq per litre Potassium 33 mg per 100 ml = 8 25 m Eq per litre Film no bacteria found, the mucinous material is stained by mucin-specific stains Culture no growth Conclusion the material consists of a mucinous high-protein fluid probably derived from breakdown of tissue cells, together with plasma transudate

(2) Pale-yellow fluid, small deposit of blood, otherwise clear Red blood-cells ++ No pus, tissue cells, or crystals Film no

TABLE III—RESULTS

—	Fluid in one or both ears at operation	Dry on stab puncture	No stab puncture	Total
Children reporting for follow-up	40	16	9	65
No still deaf	4	4	1	9
Interval since operation (mos)	18 12 34 34 Fluid still present in all 4 cases	13 28 24 12 Fluid now present in 2 cases	24	
Children not attending for follow-up	5	4	3	12
Children operated on in last 6 mos to Dec, 1947	13	3	3	19
Total	—	—	—	96

bacteria Culture no growth Protein 5 2 g per 100 ml Viscosity low A protein electrophoresis showed Albumin 54%, Globulin α1 9%, α2 10%, β 10%, and γ 17% "The protein pattern is similar to the normal serum pattern This would agree with the fluid being a serous exudate"

For comparison straw-coloured fluid from a blocked maxillary sinus was examined and reported on as follows

Yellow fluid, no obvious mucus, fibrin clot + No cells Protein 2 95 g per 100 ml Electrolytes sodium 138 5 mEq per litre = 315 mg per 100 ml, potassium 4 0 mEq per litre = 16 mg per 100 ml, chloride 104 mEq per litre = 610 mg per 100 ml This fluid has the composition of a plasma filtrate

Discussion

The importance of this interesting, elusive, and curable condition lies in the fact that it is not fully looked for in this country as a common cause of catarrhal deafness Serous otitis has many pseudonyms secretory otitis media, hydrotympanum, tubotympanic catarrh, secretory middle-ear disease, &c —indeed "serous otitis" is not a universally accepted name for this condition It was described by Politzer (1869) and Hinton (1874) Between the two world wars little was written about it, and Suehs (1952) could find only 1 case published (in 1927) in America in 1923–40

Ætiology

The cause of serous otitis is primarily a mucus block of the eustachian tube, which mucus, because it is moved down towards the orifice by ciliary action, causes a lowering of pressure in the middle ear with consequent outpouring of fluid The pathology of the fluid seems to confirm this The cause may be

(1) Fixation of the wall of the tube or blockage to its orifice by a growth

(2) Interference with tubal function by malocclusion of the teeth (Bierman and Brickman 1946)

(3) Any condition which delays the mucus lining the tube from emptying by ciliary activity into the nasopharynx—e g

(*a*) *Adenoids*—It should be remembered here what Aschan (1954) says about lymphatic tissue in the tube

> "In agreement with Eggston and Wolff it has been impossible to find any histological evidence, either from fœtal or post-fœtal material, to indicate that the lymphatic tissue of the nasopharynx ever extends as far as, still less invades, the pharyngeal orifice of the eustachian tube"

(*b*) *Nasal infection or irritation*

(*c*) *Air travel.*

(4) Otitis media, often of low virulence, treated improperly with antibiotics This may be responsible for the apparently increased incidence of serous otitis in the past few years

(5) Bullous influenzal otitis

Treatment

Treatment should aim primarily at restoring tubal patency and the normal elasticity of the tympanum by removing the fluid, and secondarily at eliminating associated causes This is not a generally accepted procedure in this country, for Bateman (1957) says about serous otitis "Once again I emphasise that myringotomy is not an essential part of the treatment of these patients"

In this series of 96 children 53 had serous otitis (Of 192 ears 78 were affected, some cases, of course, being unilateral) Of the 53 children affected 20 had thick mucus in one or both ears, and it is in this type of case that spontaneous cure is very hard to imagine One patient under my care, an adult, aged 45, had been deaf for fifteen years and had a large collection of very tenacious mucus in both ears When this was removed, his hearing vastly improved, but it is not quite normal now because of the overmobility of drumheads which has resulted from the disease

Hantman (1952) states "It, i e serous otitis, must be assiduously searched for in children, for here is a golden opportunity for reversing pathology before changes render the process irreversible with permanent hearing damage"

I am grateful to Dr C D L Lycett, medical officer of health for Wiltshire, and to his staff for their cooperation and interest, Mr E Glatz and Mr R D Owen for their generous help and advice, and Miss M Stock for her skilled assistance

REFERENCES

Aschan, G (1954) *Acta otolaryng , Stockh* 44, 295
Bateman, G H (1957) *J Laryng* 71, 261
Bierman, H R , Brickman, I W (1946) *Ann Otol , &c , St Louis*, 55, 5
Hantman, I (1952) *Bull N Y Acad Med* 28, 817
Hinton, J (1874) The Questions of Aural Surgery London
Politzer, A (1869) Diseases of the Ear
Rawlins, A G (1954) *Trans Amer Acad Ophthal Oto-laryng* 58, 427
Suehs, O W (1952) *Laryngoscope, St Louis*, 62, 998

New Inventions

A NEW NEBULISER

This nebuliser has been developed over a period of seven years in the Pneumoconiosis Research Unit of the Medical Research Council, in response to a demand for a nebuliser which was robust and easy to clean The new nebuliser not only satisfies these requirements but has a performance at least as good as that of any other similar device at present available

DEFECTS OF EXISTING NEBULISERS

When this work was begun (1951) two kinds of nebuliser were in use in the wards of the Pneumoconiosis Research Unit the 'Collison Inhaler' and various types employing a glass spray unit

The Collinson inhaler is in many respects excellent, but it has one serious defect the liquid is fed into the spray through three blind holes in an ebonite spray unit Since most liquids used in nebulisers tend to form a deposit, these holes inevitably become blocked sooner or later and are then, because they are blind, difficult to clean

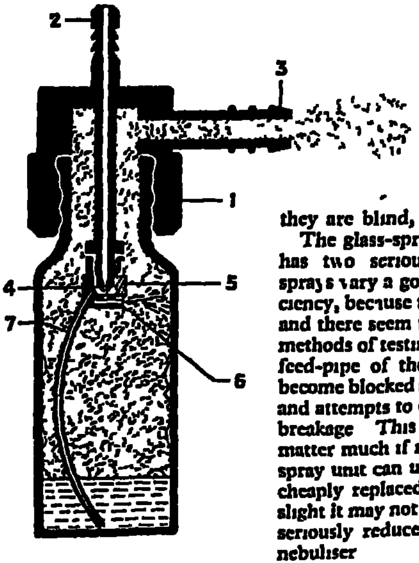


Fig 1

The glass-spray type of nebuliser has two serious defects (1) the sprays vary a good deal in their efficiency, because they are hand-made, and there seem to be no satisfactory methods of testing them, and (2) the feed-pipe of the spray is liable to become blocked after a period of use, and attempts to clear it often lead to breakage This breakage does not matter much if it is obvious, for the spray unit can usually be easily and cheaply replaced, but if damage is slight it may not be noticed, yet may seriously reduce the output of the nebuliser

Other nebulisers have since become available which to a greater or less extent overcome these defects, but only at the cost of complexity, difficulty of manufacture, and the use in some cases of metals In our experience neither chromium-plating nor the use of stainless steel or monel metal prevents corrosion, in any case many pharmaceutical manufacturers specify the use of a non-metallic spray for their products

CONSTRUCTION OF NEW NEBULISER

The nebuliser (figs 1 and 2) is made entirely of 'Perspex', which seems comparable to glass in its resistance to corrosion and freedom from ill effects on nebulised solutions, yet is at least as easy as metal to machine and fabricate in a reproducible fashion

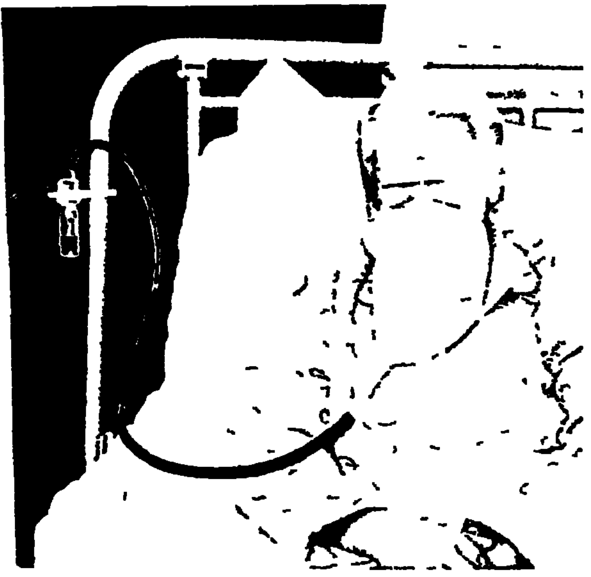


Fig 2.

The nebuliser consists of a solid cap (fig 1, 1) into which can be screwed any suitable bottle—of glass, perspex, polyethylene, or nylon

The thread is that of a glass ' Universal ' container, which is suitable, cheap, and easily obtained Universal containers are very robust, but unfortunately coloured ones are not available at present

The cap carries on its top surface the inlet connection (fig 1, 2) and on one side the outlet connection (3) The inlet connection communicates with a fine jet (4) on to which is screwed a knurled nozzle (5) This nozzle carries a circular baffle plate (6) mounted on an eccentric pillar through which passes a flexible (polyethylene or polyvinylchloride) feed-tube (7) of suitable length to reach nearly to the bottom of the bottle The nozzle has a central opening, the " throat ", which is of such a size that as the air-jet passes through it a vacuum is created which draws liquid up the feed-pipe so that it is atomised by the air-jet. The resulting spray impacts against the baffle plate and the coarser droplets (more than about 8 μ diameter) are trapped, coalesce, and fall back into the liquid

In earlier models the baffle plate was in the form of an anvil fixed in the bottom of the bottle, with its surface about 2 cm away from the nozzle, copying the basic Collison design, but recently it has been found that bringing the baffle to within about 1 mm of the nozzle considerably increases the density of the cloud A small increase in the maximum droplet size results (from 6 to 8 μ diameter) but this does not appear to be any disadvantage in practice.

The nebuliser requires a gas pressure of at least 10 lb per sq in and preferably 20 It was originally designed for a standard oxygen-cylinder reducing valve, which is set at 20–25 lb per sq in , but it can also be used, with a suitable control valve and hose, on the 60 lb per sq in piped oxygen supply that is now installed in many hospitals When connected in this way the nebuliser can conveniently be clipped to the bed with the double clip provided, as shown in fig 2

At a pressure of 20 lb per sq in the standard instrument delivers 10 litres of oxygen a minute, and nebulises about 20 ml of liquid per hour The nebuliser is not suitable for operation with a hand bulb, but can be operated off an electric pump of sufficient power

A blockage can easily be cleared by unscrewing the nozzle (5) with the fingers The blockage is usually in the annular orifice between the jet and the throat, so that once the nozzle is unscrewed it can be simply washed out

Any blockage of the feed-pipe (7) can be cleared if necessary by passing a piece of wire right through it, as it is now open at both ends, but blowing through it is usually sufficient

The jet hardly ever becomes blocked, but if it does, it can be pricked with a fine wire and cleared by blowing back up it

In addition to being practically unbreakable and easy to clean, the nebuliser appears to have as good a performance as any other on the market This has been achieved by comparing it with various other models as they became available, and copying those features which seemed to improve the performance The question of what in fact constitutes a " good " performance is at present a very open one Briefly the criterion used has been the output of droplets in the size range 1–6 μ diameter at a given gas-flow The method of determining this, and its justification, will be discussed in a later publication

In addition to its use for producing therapeutic aerosols, the nebuliser can be used as a humidifier With water in the bottle, and cylinder oxygen, which is practically dry, it produces more than 100% humidification This compares favourably with the usual bubbler devices which, unless heated, never raise the humidity above 50% The disadvantage of using the nebuliser as a humidifier with the usual methods of administration of oxygen is that the relatively high pressure upsets the calibration of the flow-meter supplied for use with the low-pressure bubbler type humidifier This can, however, be rectified by the use of an appropriate correction table, obtainable from the makers

I am grateful to Dr J C Gilson and the staff of the Pneumoconiosis Research Unit for their constant help and encouragement, and especially to Mr V Gubb who made many models of the nebuliser The drawing was prepared by Mr W H Roberts, and the photograph was supplied by Messrs Richard Daleman of 325, Latimer Road, London, W 10, who are the makers

National Institute for Medical Research,
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B M WRIGHT
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Reviews of Books

Neuropathology

J G GREENFIELD, M.D , F R.C P , consulting pathologist, National Hospital for Nervous Diseases, London, W BLACKWOOD, M B , F R C S.E , M.R C.P E , pathologist, National Hospital for Nervous Diseases, London, W H MCMENEMEY, D M , F R C P , pathologist, Maida Vale Hospital for Nervous Diseases, London, A MEYER, M D , emeritus professor of neuropathology (Institute of Psychiatry), University of London, R M NORMAN, M.D , M R C.P , neuropathologist, Burden Mental Research Department, Frenchay Hospital, Bristol London Edward Arnold 1958 Pp 640 105s

WE have long been waiting for a substantial yet accessible textbook in the English language, in which the accumulated knowledge of the histopathology of the nervous system is integrated and presented critically No-one was better qualified to undertake such a work than the late Dr J G Greenfield, and he and his colleagues have produced a book which promises to remain the standard work of reference for many years to come

All aspects of the pathology of nervous and mental diseases are included, with the exception of tumours Dr Greenfield has provided most of the chapters, and particularly valuable is his introductory account of the normal and abnormal cytology of the neurone and neuroglia, and the sections on infections, trauma, demyelinations, system degenerations of the brain-stem, cerebellum, and spinal cord, and peripheral neuropathies, in which he has distilled the essence of his profound experience He has been helped by several contributors, each one eminent in his own subject Professor Blackwood on vascular diseases, Dr McMenemey on dementias, Professor Meyer on anoxias, intoxications, epilepsy, and psychoses, and Dr Norman on prenatal malformations, birth injuries, and diseases of early life

A historical appraisal of Alzheimer's disease and accounts of the effects of atomic explosions and ultrasound waves illustrate the book's range, and neurological topics in the forefront of present-day interest, such as hypertensive cerebral disease, the blood-brain barrier, carcinomatous neuropathy, temporal-lobe epilepsy, the anatomical basis of prefrontal leucotomy, and the nosological problems of diffuse cerebral sclerosis, are authoritatively discussed within the general framework The lesser-known ways of neuropathology are also explored, and the practising neuropathologist in particular will welcome the detailed account of the primary dementias, and Dr Norman's clear and beautifully illustrated survey of a subject in which the disciplines of classical histopathology still promise rich rewards

This handsome book contains over 500 illustrations of high quality Each chapter has its own bibliography, and there are some 2500 references in all The authors' hope that their labours will give the neurologist and psychiatrist that basis for diagnosis and logical treatment which only pathology can supply is fully realised Not only the pathologist but the neurologist, the neurosurgeon, and everyone working in the neurological sciences will find the book an indispensable source of knowledge To Greenfield, who did not live to see its publication, it stands as a memorial worthy of a life rich in achievements

Principles of General Surgical Management

H A F DUDLEY, F R C S E , lecturer in surgery, University of Edinburgh Edinburgh and London E & S Livingstone 1958 *Pp 203 27s 6d*

IN this newcomer to the important range of books on what is sometimes inappropriately called "minor" surgery, Mr Dudley has used the term surgical management in the title, and this fails to do justice to the contents since many of the methods he describes would be required in medical wards Moreover, the book is concerned with more than principles, it is in fact one to which a student or a newly qualified man could confidently turn for exact direction in such procedures as lumbar puncture, the application of plaster-of-paris, venepuncture, catheterisation, and so on Clear directions and information are also given on more general topics, including nutrition, shock, and electrolyte therapy, and in this respect it is good to record that the book is up to date (corticoid therapy and the effects it may have when surgery is undertaken have been included) The book ends with a chapter on side-room and investigative work, which is a useful collection of the methods required for the common investigations of urine, blood, and other biological fluids One criticism this is a book to be tucked away in a convenient place for ready and rapid reference, but its shape is such that a shelf is required—or a poacher's pocket It is not long, and more convenient proportions may be possible in a later edition

The Biologic Basis of Cancer Management

FREDDY HOMBURGER, M.D , research professor of medicine, *Tufts University School of Medicine, Medford, Massachusetts* London Cassell 1958 Pp 354 75s

IN forewords to this book Dr L V Ackerman, Dr C C Little, and Dr A Ochsner emphasise the need to bridge the often very wide gulf between experimental cancer research and its clinical applications They believe that the book will do this and so broaden the knowledge and outlook of specialised research-workers and also help all doctors interested in cancer and concerned in its treatment

With some reservations, this claim is justified The book's principal advantage over collections of specialised essays lies in its more connected plan, the experimental and clinical aspects are usually developed in successive chapters and then an attempt is made to correlate them whenever possible The drawback, of course, is that no one author is likely to be uniformly successful in covering such an enormous range and he cannot hope to satisfy every specialist worker Even if he avoids factual errors (and there are not very many in this book), a successful balance of emphasis can be achieved only by a critical selection of the data, and that calls for an outstanding grasp of the whole subject Understandably, Dr Homburger has not wholly succeeded in reaching this high standard, indeed he mentions that the idea of this book was rejected by one publisher, who was advised that no one person could write it Consequently, it is to some extent a "review of reviews," fortified by judicious selection, sensible comments, and sound and detached judgment, without pretension to any particular originality

One of its most valuable features is a series of tables summarising the main points detailed in the text Such tables cover, for instance, environmental carcinogenic agents and corresponding cancer sites, details of some of the principal carcinogens, lists of tumours in which chromosomal influences are prominent, neoplasms of endocrine organs, changes in the tumour-bearing host, and a long summary of the natural history and clinical course of a wide range of human cancers

The book is in four parts ætiology, biological properties, diagnosis, and treatment Ætiology is taken to include all causative factors such as the hereditary background, environment, and the influence of viruses and hormones Chemical carcinogens are adequately reviewed, but on p 32 the footnote should refer to benzpyrene and not benzanthracene The device of working backwards—for instance, from Andervont (1942) to the discovery of hepatocarcinogens (Yoshida, 1931)—is used at various points and is rather irritating, and so is the way that the references (generally very good) to each chapter are congregated at the end of the book, without any chapter numbers on the page-headings, either in the text itself or in the reference pages at the end Treatment (including prevention, surgery, and radiotherapy) receives only 28 pages, among which chemotherapy, generally considered to be a promising prospect as well as one of great theoretical interest, gets only 12 pages

Nevertheless, the book as a whole is good and will probably achieve its aim

Principles of Ophthalmoscopy

JOHN K ERBAUGH, M D Norristown State Hospital, Norristown, Pennsylvania Springfield, Ill , Charles C Thomas Oxford Blackwell Scientific Publications 1958 Pp 69 42s

THE details of pathological change in the retina—vascular sclerosis, microaneurysm formation, increased exudation, and frank hæmorrhages—are probably of greater value in identifying the responsible systemic disease than are the pathognomonic pictures of established retinopathy seen in the later stages, and the value of this small book of four chapters rests chiefly on the emphasis it lays on these points Preliminary detection of opacities of the media with the ophthalmoscope is helpfully described, and the details of the normal fundus are considered at length, before the changes seen in the pathological disc, vessels, and fundus generally are reviewed

The general form of the book is attractive, but it seems a pity that more of the excellent colour photographs were not included in place of the coloured diagrams, useful though these are

A Study of the Major Psychoses in an English County

Maudsley Monographs, no 3 MICHAEL SHEPHERD, D M , D P M , senior lecturer, Institute of Psychiatry London Institute of Psychiatry and *Chapman & Hall 1957 Pp 159 25s*

THE applications of statistical methods in psychological medicine have been mainly concerned with assessing improvement under different kinds of treatment, and little attention has been paid to the vital statistics of mental disease

Dr Shepherd here compares the admissions to a county mental hospital for the two triennia 1931–33 and 1945–47 The study is based on examination of the administrative and clinical records of 1223 patients followed for five years after their admission The results show a striking difference in the number and type of admissions during the two periods, and an improved outlook, assessed in various ways, for patients entering hospital during the second period Only the most tentative conclusions can be drawn about the factors that may have contributed to this change

The book shows the drawbacks and limitations of this type of retrospective investigation, and draws attention to the importance of carrying out a well-planned and long-term prospective study of a similar kind Dr Shepherd presents his material well and succeeds in making his mass of figures easy both to understand and to read

THE LANCET

LONDON 5 JULY 1958

The Partnership

“ My job ”, said the Minister of Health ten years ago, “ is to give you all the facilities, resources, apparatus and help I can, and then to leave you alone as professional men and women to use your skill and judgment without hindrance Let us try to develop that partnership from now on ” Since July 5, 1948, the partnership of which he spoke has been strained sometimes to breaking-point, but its development is still perhaps the chief need of the National Health Service For the N H S is something quite different from the conventional State medical service in which the doctor takes orders from Authority it is simply a legislative device by which doctors can continue their work without charging fees and by which the nation's insufficient medical resources can be used to better advantage In organisation and planning to these ends, the most valuable initiative and ideas will often (though not always) come from the people who actually look after patients, but, on the other hand, planning and organisation may weaken professional responsibility and professional enthusiasm unless these people feel that they can have an effective part in it whenever they choose Though they will do all they can for their own patients, they may take no interest in the service as a whole, and in its evolution, unless it specifically offers them participation and hence a chance of getting the results they want To have a sense of partnership in it they must know that their voice will be heard, and heeded, by an administrator who shares the Ministerial concept of his job

For our part we think the National Health Service one of the biggest improvements in the life of this country since the war Thanks to very hard and intelligent work by a great many people, professional and lay, it has done much to better the conditions of medical care, especially in hospital, and it has been an immense comfort to the public But, after only ten years' experience, any jubilation must be at best provisional, for the initial gains to be expected from more rational organisation would be bought too dearly if the cost were an eventual decline in the spirits of the people whose work is organised Even today, unfortunately, the morale of many who take part in the service is not as high as it ought to be in its new bottles some of the wine that should be sparkling has gone flat or even sour Where there is evidence of such depression or disappointment, especially among the young, it should be taken very seriously indeed One of the reasons for it is obvious, and needs only passing mention here because it has become the subject of a Royal Commission Mr Bevan, in his message of ten years ago, said that when fees were abolished the new situation must not mean “ any unfair worsening of a doctor's material livelihood ” This, he said, was vital, and he was right yet the worsening has taken place, and virtually all of us would describe it as unfair Indeed, most of us think that the Treasury has taken advantage of inflation to reduce remuneration in the service—as compared with remuneration outside it—to levels more convenient than those that had been negotiated, and we think that successive Governments have been less than straightforward in their treatment of those who entered a national service at the nation's request This, however, is not the cause of the vaguer but deeper malaise which found expression in a letter we reproduced from the Widdicombe File a month ago[1] The complaint of that letter was essentially that the status of the doctor, as partner in the service, is depreciating and this, we fear, is true We have never been among those who held that hospitals, for example, belong to the medical staff, who can do what they like with them, but we suspect that the pendulum has now swung too far towards lay management of medical affairs, and that consequently the service stands to lose much that doctors ought to be giving it—and which in fact nobody else can give

Though lay intention cannot be wholly excluded, the main reason why most doctors now feel “ out of it ” is the elaboration of administrative machinery Of course, the N H S is a very big, as well as a very complex, organisation, and big organisations always tend to induce bureaucracy—whether the environment is that of Melbourne or Moscow, Manchester or Milwaukee Nevertheless, the British are said to be very good at streamlined organisation when they really give their mind to it So let us examine, if briefly, some of the means suggested for making the administration of the N H S more appropriate to its purpose, and more efficient

THE MINISTRY

The first suggestion, often made in the '40s and lately revived, is that the service should be run by an autonomous national corporation, comparable to the B B C Unhappily, though attractive to the professions, this is constitutionally impossible a body which spends hundreds of millions of public money, which it does not itself raise, must be controlled by a Minister answerable to Parliament On the other hand, there is no constitutional reason why the Minister who looks after the health service need have a department so unimaginatively similar to other Government departments as it is at present Twelve years ago, when the service was entrusted to the Minister of Health and Local Government, the disadvantages were offset by the fact that this was a relatively important department, whose chief had an influential position in the Cabinet, but, when Local Government was removed from it and the residual Ministry was confined to medical affairs, the opportunity might have been taken to redesign it on less conventional lines—recognising that it is the administrative nucleus of an entirely novel kind of public service Even now such reconstruction ought to be considered, and we do not think we are offering a merely medical view when we say that the Ministry would be better suited to its unusual functions, as well as being more acceptable as the head office of the service, if its professional element were strengthened. Repeatedly we have hoped for a Minister who would show himself as the perpetual champion of the service, but, though many Ministers have fought its battles against the Treasury, their duty in public is, on the contrary, to represent the Government—to explain (as a rule) why things cannot be done. Besides, regarded as representative of the service, the Minister has the demerit of continually moving on. Nor can we expect the secretary of the Ministry, though permanent, to assume the role of either titular head or chief officer of a medical service. Is it then really impossible that in this particular Ministry the chief permanent official should be a professional man? Since the subject we are discussing is morale, which depends on people's feelings (rational or irrational), we must say frankly that professional people in the service would regard its control as less remote if it were not so emphatically lay.

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[1] *Lancet*, June 7, 1958, p 1221

Again, though the Ministry and its servants have done distinguished work in the creation of the service, and have shown both courage and insight in coping with the extraordinary difficulties of its first ten years, their very immersion in its daily affairs hinders their sitting back and forming long views on its development. This was to have been the task of the Central Health Services Council, which in the plans for the N.H.S. was accorded high importance as both a representative and a planning body—being, indeed, described as the brain of the service. But, because of its large size, diverse constitution, and infrequent assembly, the Council has not been found really suitable for this major responsibility, and, though many of its committees have given farseeing advice on particular problems, the Ministry has never used the Council in the way intended, or encouraged it to become a creative force. Planning, in the sense of deciding priorities, has mostly been kept within the Ministry itself, and unquestionably much wisdom has been shown. Many of the achievements of the service owe much to the Ministry's steady pressure—big ones such as the improvement of mental hospitals and the better care of old people, and small ones such as the more frequent visiting of children in hospitals. For general practice it has favoured the practitioner's direct access to pathology and X-ray departments and has promoted the idea of the family doctor as leader of a medical team, and, if its approach to the renaissance of general practice has been more cautious than some of us could wish, we must respect Dr GODBER's explanation (p. 2) that "it would not be right to attempt to formulate a plan for the development of general practice centrally and then impose it." Nevertheless, valuable though this leadership has been, we have never felt sure that the Ministry was facing the underlying issues of the service and had reached a policy for its development as a whole. Do the hospitals, public health, and general practice receive the right share of our resources? If not, what needs to be done to shift responsibilities and burdens and manpower from one to the other? If, for the sake economy and efficiency, contraction of effort is needed at one point, and expansion at another, do the professional and financial incentives in the service promote the desired changes?[2] Rightly or wrongly, we suspect there are still some big lacunæ in the policy of the service and some inconsistencies in its application, and, if the Central Health Services Council is not the right body to study them, the planning capacity of the Ministry might perhaps be strengthened by the appointment of a smaller group—say, half a dozen experienced but not too elderly people, paid a half-time salary, and with access to whatever secretarial and statistical help they want—who would be charged with keeping the policy of the service under continuous review. Nothing much, at any rate, would be lost by trying the experiment, and if such a group were prepared to receive and consider constructive criticism they would also fulfil the incidental but very necessary function of providing an address to which reformers and dissidents could usefully post their suggestions and objections.

BOARDS AND COMMITTEES

Whether or not the machinery of the Ministry needs to be supplemented, there can be no doubt that the machinery of hospital administration needs to be simplified, and an inquiry into it could properly be started soon, before any more interests have time to vest.

Those of us with fairly long memories will recall that hospital regions and hospital groups were both originally conceived for the same general purpose—to get the hospitals of an area to play as a team instead of individually. After much discussion, in which the regions were sometimes to be large and sometimes small, both boards and management committees were put into the service, but possibly this was no more than an example of the extravagant generosity of the times, and we might get on just as well or better without one or the other? From time to time, abolition of the regional boards has been proposed, but, if one is to go, we should ourselves be inclined to eliminate the management committees. Regional boards have acquired, for better or worse, more administrative functions than, as planning authorities, they were meant to have, and, if the number of these boards was doubled, so that the average size of regions was halved, each should be able to maintain direct contact with all its hospitals individually. Day-to-day management would revert to the house committees, which would thus regain their soul, and those hospitals and institutions that have a genuine need to work in close association could link themselves by less formal and elaborate means than a common administration. In this way one of the three tiers of hospital administration could probably be taken out without endangering the structure, and the amount of time and trouble this would save would be enormous.

Even so, the simplifying process should not stop there, for perhaps as much good, or more, could come of fresh examination of the constitution of the boards and committees themselves. We should not be surprised to find that at least half their work arises from their being too big, for a big board or committee, meeting only occasionally, can seldom reach a decision on any important problem except by referring it to a committee which can go into it more carefully Unfortunately (if we may propound a variant of PARKINSON's law [3]) the amount of work increases with the number of *committees* available for its completion Certainly it has been very helpful to the N H S that so many able people should have been willing to give up so much time to the conduct of its boards and committees, burning gallons of midnight oil over its interminable agenda, and something would as certainly be lost by having smaller boards which would contain less variety of experience. Yet the gain in expedition and labour would be quite immense if (as TAYLOR suggested years ago [4]) the regional boards were reduced to an average of eight members, meeting often enough to be fully familiar with their business and able therefore to take the decisions themselves They would have to be paid an honorarium of course, and a big one: but their job would, after all, be no less important than that of the executive directors of other big concerns, and if the Government want the best people for such work they cannot sensibly limit their choice to the rich or retired.

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[2] *Ibid* 1956, i, 237

THE UNITED VOICE

How would such streamlining of hospital administration affect the partnership we are advocating? Clearly, it would reduce the likelihood of doctors serving on the executives, and would thereby disappoint those who want to see the professions heavily represented on the boards and committees which administer the service But in our view the demand for this kind of professional representation is and always has been misguided [5] A board ought, naturally, to give more weight to the views of a medical advisory committee, presented unitedly, than to those of its individual medical members, who are (or should be) appointed for their personal qualities and not as experts or as accredited representatives of the hospital staffs But in practice the layman will inevitably be confused if he receives medical advice from two quarters, and the influence of the advisory committee can easily be weakened by the presence of doctors on the board, who may speak with a different voice. Indeed, the result may be that the board, getting divergent guidance, will feel free to take its own line Unless therefore, the professions are granted absolute majorities on the boards (which seems improbable) they will do best to concentrate on providing, for each executive, an advisory committee which is in a position to offer a considered opinion on behalf of the professions concerned. If the chairman of this committee, sitting with the executive as a non-voting member, produces an expert opinion of this kind, his board will think at least twice before ignoring it To go on trying to make the boards themselves representative of everybody and everything will mean that they get bigger rather than smaller, and that they do their work through even more committees The proper course, as we see it, is to reduce the administrative bodies both in number and in size, but to make sure that each of them, in deciding matters of moment, has the benefit of a corporate professional opinion

PROFESSIONAL INITIATIVE

If it were true that our profession had been nationalised (as people so often and so wrongly assert), doctors would be able to influence the service only through these official channels But in point of fact, though most medical men and women work in contract with public bodies, the profession has a separate and thriving independent life, based on its own societies and institutions We cannot too often repeat that in this country doctors are *not* State officers or Civil Servants, and it would be a great pity if, even within the service, they began to feel that initiative must always come from the centre rather than the periphery For example, those who think that general practitioners ought to have part-time hospital appointments need not wait for an administrative circular but should set about seeing whether and how what they want can be arranged in their own areas, for that is how new things are still most often done. A more vigorous suggestion we have heard is that, instead of reflecting negatively on the defects of a tripartite service, local doctors from all branches should form a small unofficial group of their own—to look into what is wrong in their area and to make sure that it is put right. A really active ginger group of this kind might (for intraprofessional reasons) find it convenient to meet anonymously and remotely, hooded and at midnight, but no such anxious considerations need deter those of more academic or timorous habit who prefer to make their criticisms of the service, and their proposals for its amendment, through their associations, colleges or faculties. In the past year many of the principal professional bodies have set out some of their opinions in memoranda of evidence to the Royal Commission on Remuneration, but in general their corporate capacity for constructive thinking on the medical services is too little cultivated The British Medical Association hopes to undertake a review of these services, which should be invaluable if it rivals in foresight the report of the Association's Medical Planning Commission before the war Exceptionally well placed for making background studies of medical policy is the Royal College of Physicians of London which could helpfully produce more of the documents with which it has sometimes stimulated professional discussion In promoting the development of the service, King Edward's Hospital Fund and the Nuffield Provincial Hospitals Trust (whose latest progress report appears this week [6]) have contributed ideas as well as money Of all the King's Fund contributions, none perhaps will do more good in the long run than its Administrative Staff College, where partnership is seen and presented as a necessity On p 42 Dr. W S PARKER suggests that there should also be a general staff college which could give young doctors an administrative understanding that would later help them to help the service Unquestionably medical knowledge, in its growing complexity, will not be fully applied unless quite a lot of members of our profession are led to take a special interest both in what CLARK [7] calls administrative therapy and in the larger subject of therapeutic administration.

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[3] Parkinson, C. N. Parkinson's Law London 1958

[4] Taylor, S. *Lancet*, 1951, i, 725

[5] *Lancet*, 1951, i, 710

[6] A Record of the Progress of Schemes and Descriptions of New Projects 1955-58. Fourth Report. Nuffield Provincial Hospitals Trust Nuffield Lodge Regent's Park, London, N.W.1

Among national organisations, the N H S is remarkable because it represents a new kind of partnership between the State and the professions its purpose is to enable people to work effectively to their own professional standards This partnership breaks down if either side disclaims responsibility—for instance, if a doctor, conscious of some remediable administrative fault which is lowering the quality of his work, does nothing more positive than blame "the service" Such dissociation of the administrative and professional parts of the undertaking always does damage, for discontent without appropriate action is anything but divine Moreover, the truth is that, though administrators have been slow in solving some of the problems of the service, there are others which only the medical profession itself can solve The rigid and routine nature of training for specialties, and the barriers between them, are the result of professional policies—and policies by no means confined to this country Is it the administrators of the N H S who are making it so difficult for young men to have the useful experience of going for two or three years to one of the Commonwealth countries where they are so badly needed? How much of the difficulty of getting into general practice has arisen because practitioners no longer set sufficient store by postgraduate hospital training? Even the problem of the senior registrars and the S H M O S is presumably insoluble—whatever the Government do—until consultants make up their mind about the advantages and disadvantages of a swelling of their ranks, with perhaps a consequent diminution in their prestige Looking round at the many difficulties of the service which obviously demand some fresh approach, it seems that the best means of making progress would be a statutory period of amnesia in which all of us forgot what we had ever said before Meanwhile, however, we make no apology for recalling and repeating the plea for partnership which appeared in our editorial of July 3, 1948

"If we continue to think of the National Health Service as a State service it will fail, but if we recognise it as our own service we can make it a great and increasing success"

The Ætiology of Leukæmia

FOUR years ago we reviewed the work of LUDWIK GROSS on transmissible mouse leukæmia [8] GROSS used for his experiments two contrasted *inbred strains* of mice, the Ak strain, 70% of which develop lymphatic leukæmia at the age of 7–10 months, and the C3H strain in which the incidence of spontaneous leukæmia is only 0 5% Cell-free filtrates were prepared from the organs of leukæmic Ak mice, when these were inoculated into newborn C3H mice, less than 24 hours old, nothing happened immediately and no tumour developed at the site of inoculation, but in the mouse's middle age (the normal life-span is 2½–3 years) 81% of these mice developed leukæmia, if the inoculation was delayed until the mice were 2–6 days old, only 55% became leukæmic, and if the inoculated mice were more than 7 days old, no leukæmia occurred GROSS also showed clearly that whatever was transferred from the leukæmic Ak mice caused leukæmic changes in the C3H cells themselves, since the C3H leukæmia could only rarely be transplanted back into Ak mice GROSS concluded that the lymphatic leukæmia in Ak mice was caused by an agent transmitted through the embryos from one generation to the next, and, since not all mice carrying the agent develop leukæmia, and some may die from other causes after they have transmitted the agent to their offspring, true hereditary transmission may be simulated When GROSS attempted to prove that this leukæmic agent was filtrable, some odd results appeared If the material was filtered through Selas microporous porcelain, quite a lot of the inoculated newborn C3H mice developed parotid tumours at an average age of 3 3 months, instead of leukæmia at about 10 months On the other hand material filtered through Berkefeld N candles produced mostly leukæmia and a few parotid tumours These unexpected findings clouded an otherwise clear story

On the whole these results have been confirmed by others, [9–11] and several new points have emerged [12] The transmissible agent from the Ak mice has been found to induce subcutaneous fibrosarcoma in some animals as well as parotid tumours in others This finding underlines the oncogenic potentialities of the agent But GROSS found that, using a particular inbred strain of mice, only leukæmia was produced by inoculation and tumours did not appear [13] A more surprising experiment showed that cell-free extracts from tissues of apparently *normal* Ak (or similarly leukæmia-prone C58) mice inoculated into newborn C3H mice could induce leukæmia and, in a few instances, parotid tumours [14] Further experience has shown that there is considerable variation in the potency of the leukæmogenic agent and in the susceptibility of the hosts even among inbred strains When this was realised potent agents were selected for study, and it was found that the potency could be increased by cell-free passage through generations of C3H mice GROSS has now developed a leukæmogenic agent that will induce leukæmia in up to 97% of inoculated suckling C3H mice 1–14 days old after a latent period of only 3–4 months

The technique of using newborn mice less than 1 day old for the inoculation of tumour-producing agents has now been adopted by several laboratories, and some curious results have been reported GRAFFI et al [15] prepared filtered extracts from Ehrlich mouse carcinoma and some other tumours, and inoculated them into a strain of mice known to have an incidence of spontaneous leukæmia of less than 1%, 34–75% of the inoculated mice developed myelogenous leukæmia after a latent period of 4–8 months Friend[16] obtained similar results and showed that the myelogenous leukæmia could be transmitted by inoculation of cells into adult mice of the same strain This phenomenon of induction of leukæmia by cell-free extracts from tumours is the reverse of Gross's induction of tumour growth by inoculation of leukæmogenic agents Gross considers that these findings emphasise the importance of variation in the recipient, and points out that parotid tumours develop from leukæmic filtrates only when the inoculated host is less than 16 hours old; above this age, only leukæmia appears

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[7] Clark D H *Lancet*, 1958, i, 805

[8] *Lancet*, 1954, i, 101

[9] Woolley, G W, Small, M C *Cancer*, 1956, 9 1102

[10] Furth, J, Buffett, R F Banasiewicz-Rodrigues, M, Upton, A C. *Proc Soc exp Biol*, N Y 1956 93 165

[11] Dulaney A D, Maxey, M, Schillig, M G, Goss, M F *Cancer Res* 1957, 17, 809

[12] Gross, L *ibid* May, 1958

[13] Gross, L *Proc Soc exp Biol*, N Y 1954, 86, 734

[14] Gross, L *Cancer*, 1956 9, 778

[15] Graffi, A, Bielka, H, Fey, F *Acta hæmat* 1956, 15, 145

A set of experiments supporting the hypothesis that the leukæmogenic agents are viruses have been reported by Stewart and her co-workers[17] They showed that the leukæmic agents could be grown in tissue-culture on mouse kidney or chicken chorion allantois and would then induce parotid tumours, but not leukæmia There are some other properties that support the virus hypothesis For example, the material can be stored without loss of potency at —70°C for $3^1/_2$ months or so, studies with the ultracentrifuge suggest that the leukæmogenic particles are about 50–70 mμ in diameter, and electron microscopy shows particles of a somewhat similar order Extracts filtered through membranes of 340–200 mμ porosity can induce leukæmia, but extracts filtered through membranes of 140–93 mμ porosity still induce parotid tumours[18]

To explain all these findings Gross[19] proposed the hypothesis of "vertical transmission" of a pathogenic agent By this term he means the transmission of extraneous pathogenic agents from one generation to another by germinal cells or occasionally, as in the mammary carcinoma of mice, through the mother's milk This contrasts with the usual methods of transmission of infectious diseases by contact, by food, through the air, or through the agency of insect or other vectors In these known methods of transmission, the transfer takes place in a few days or weeks, and thus the spread can often be traced without difficulty But "vertical transmission" works differently, and according to Gross has the following characteristics

The pathogenic agent, transmitted by the germinal cells or the mother's milk, may remain latent for a considerable portion of the host's life-span so that the infected animal appears in perfect health but can still transmit the seeds of disease to its offspring, thus C3H newborn mice receiving the pathogenic agent from Ak mice do not develop leukæmia till middle age, and by then they have mated and may have passed on the disease, via the germinal cells, to their own offspring Sometimes the agent may not become activated at all during the lifetime of the host, and in some instances an agent is harmless for its own carrier host but can cause fatal disease when transferred to another strain or species Gross points out that several examples of this type of transmission are known in nature (e g, *pebrine*, the silkworm disease studied by Pasteur, mosaic disease of potatoes; and Rocky Mountain fever and tularæmia transmitted through the eggs of tick vectors) Certain types of bacteriophage are also transmitted from one generation to another, Lwoff[20] showed that bacteriophage may remain dormant until activated by certain agents, including X rays, and once activated the phage may destroy its own host by lysis The activating agents for leukæmia are hardly known, we suspect that ionising radiations and chemical poisons such as benzol may have this effect, but we have no idea how they work or what is the nature of the change induced in the transmitted pathogen

In four years, then, Gross has consolidated the evidence for the "vertical transmission" by cell-free agents of mouse leukæmia and certain mouse tumours, and it is likely that chicken lymphomatosis is similarly transmitted But whether these ideas can be applied to human leukæmia is doubtful Gross himself points out that the evidence will be hard to get. Clearly human leukæmic material cannot justifiably be inoculated into newborn infants Tracing an agent transmitted vertically requires the study of several generations, human leukæmia was recognised as a distinctive disease only a century ago, and its modern study with reasonably accurate case-finding dates back hardly a generation Another difficulty, raised by the fact that tumours as well as leukæmia can be produced by inoculation of material from a single source, is that we do not know whether we are dealing with a single agent with varying potentialities, or several agents transmitted at the same time Four essential conditions seem, on Gross's theory, to be needed for the development of leukæmia[19] (1) inherited susceptibility of the host, (2) the presence from birth of a leukæmogenic agent, (3) an activator that may be intrinsic (metabolic or hormonal) or extrinsic (physical or chemical), and (4) conditioning of the host to allow the activators to stimulate the pathogenic agent to produce leukæmia (or tumour) So far as human leukæmia is concerned, we know hardly anything about these points We have no means of detecting whether a pathogenic agent has been transmitted or is still present in the parents of the leukæmic patient, and all we know of activation is some suggestive evidence that exposure to X rays or other ionising radiation can be followed by leukæmia[21] and that certain chemicals may act in a similar way

Despite the impasse that study of the viral transmission of leukæmia and tumour formation seems to have reached for the moment, this work is clearly of immense interest. But to the physician dealing with the leukæmias, the interest after four more years' research remains academic Indeed, if Gross is right, we are faced with an undetectable leukæmic agent transmitted at birth which becomes active in a set of circumstances at present undefined. Such a theory holds out little hope of therapeutic advance.

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[16] Friend C. *J exp Med* 1957, 105 307

[17] Stewart, S E, Eddy B E, Gochenour, A M, Borgese, N G, Grubbs, G E *Virology*, 1957, 3, 380

[18] Gross, L *Ann N Y Acad Sci* 1957, 68 501

[19] Gross, L *Blood*, 1954, 9 557

[20] Lwoff, A *Ann Inst Pasteur*, 1953, 84, 225

[21] *Lancet*, 1957, i, 1130

Annotations

NEUROLOGICAL COMPLICATIONS OF ASIAN INFLUENZA

In the recent epidemic of Asian influenza the illness was usually neither severe nor lengthy, but in a few of the enormous number of cases complications developed, some of which involved the nervous system These neurological complications are discussed in four contributions that appear on earlier pages of this week's issue Encephalitis is perhaps the best established of them Commonly it arises about the fourth to tenth day after the onset, when the patient seems to be recovering or to have recovered from the initial illness, and it is characterised by impairment of consciousness with bilateral extensor plantar responses and few or no localising signs In the purely encephalitic cases the cerebrospinal fluid (C S F) is normal The electroencephalogram (E E G) is extremely abnormal with pronounced delta activity which may be continuous or occur in bursts on a predominantly flat record The patient's condition may be critical, but recovery is usual and in most cases complete Other types of encephalitis attributed to Asian influenza include encephalomyelitis and an ataxic encephalitis [1] similar to that which may follow chickenpox It may, however, also present as a psychotic outburst in which the patient becomes restless, noisy, and violent In these outbursts the E E G is grossly abnormal with distinct delta activity, justifying the view that they are a symptom of encephalitis and do not represent a latent psychosis which has been revealed by a generalised infection

Observers from Bombay [2] to Birmingham and Barbados to Jerusalem believe that their cases of encephalitis were due to Asian influenza, and many will agree with them, but it is difficult to prove the connection beyond doubt Clinical evidence can be supported by antibody titres indicating that Asian influenza coincided with encephalitis, but Dr Flewett and Dr Hoult (p 11) show that this evidence must be evaluated critically They point out that when the cases arose there was an epidemic of influenza in the neighbourhood, and there was therefore a good probability that any person in the region would show evidence of recent infection, and that this probability was even greater in the hospital population than in the general population Nevertheless, viewing the evidence as a whole, it is reasonable to conclude that the encephalitis is the result of the influenza Whether the encephalitis is due to the presence of the virus in the brain, to activation of some other organism by the influenzal virus, or to the provocation of an allergic reaction is unknown This problem arises in other forms of encephalitis, such as those associated with mumps, chickenpox, and vaccinia

Another complication of Asian influenza is aseptic meningitis, which may be found with or without encephalitis Udani et al [2], describing influenza in children in Bombay, report 5 meningitic, 5 encephalitic, and 11 mixed cases Acute polyneuritis has also been described in association with influenza, and 2 cases are described by Dr Flewett and Dr Hoult which might be attributed to Asian influenza But here the specific relationship is much less clear, and it will probably further confuse the problem of the ætiology of polyneuritis if influenza is regarded as a specific cause

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[1] Horner, F A *New Engl J Med* 1958, 258, 983

[2] Udani P M , Athavale V B , Sayed, B A *J of J J Group of Hosp and Grant med Coll* 11, 288

MENTAL HEALTH AND NURSERY-SCHOOLS

In a nursery-school the easy introduction of the 3-year-old to a wider society is an "upward extension of the family rather than a downward extension of the primary school," [1] and sets a pattern for good relationships in the future It is not surprising that those in charge of child-guidance clinics and others who have to care for children with special problems—for example, the partially deaf—wish to secure the admission to nursery-schools of some of the children The character of nursery-schools would, however, be changed if too great a proportion of handicapped children were admitted and they ceased to cater for a cross-section of the community

At a recent conference in London of the Nursery Schools Association, the part that these schools could play in the promotion of mental health was examined against the background of financial restrictions Even in London there are places for less than 10% of the children between 3 and 5 Teachers from nursery-schools described, as did Taylor twenty years ago,[2] the problems of young mothers in suburban communities, as well as the frightening anxieties of the mother beleaguered in her 16th-floor flat while her son plays in the asphalt jungle below It is to the credit of the education committees of London and Bristol that between financial crises they have been able to slip planned nursery-schools into the ground-floors of some of the new blocks of flats We may need nursery-schools as well as colleges of technology in the coming years

PENICILLIN AND CHLORAMPHENICOL

The action of penicillin is primarily bactericidal, whereas that of chloramphenicol is primarily bacteriostatic In a summary of evidence from in-vivo and in-vitro experiments Jawetz and Gunnison [3] showed that the effect of combining two such agents is unpredictable The result depends on the relative amounts of the two antibiotics in the combination and on the organism's sensitivity to the bactericidal drug That antagonism between antibiotics may be a clinical reality hazardous to the patient was shown by Lepper and Dowling,[4] who reported that when penicillin and chlortetracycline were used together in the treatment of pneumococcal meningitis 79% of patients died, whereas only 30% of patients died when penicillin was given alone in the same doses

Many in-vitro studies of the action of penicillin and chloramphenicol in combination against a number of bacteria demonstrated antagonism, especially when the test organism was a gram-positive coccus, but others did not confirm this and some even revealed synergism These conflicting observations probably result from the diversity of in-vitro methods and the variety of test organisms and from the different ways in which the experimental results were interpreted The results of in-vivo experiments are also inconclusive In the therapy of experimental infections in mice, these two agents were antagonistic when treatment was restricted to a single injection of the drugs [5 6], but these single-dose experiments do not reproduce the conditions in which antibiotics are used clinically Speck and Jawetz [7] reported that penicillin and chloramphenicol, administered daily by intraperitoneal injection for five days, were antagonistic in the treatment of a subacute streptococcal infection induced in mice by the intramuscular injection of *Streptococcus pyogenes* But when Ahern et al [6] treated the infection produced in mice by the intraperitoneal injection of *Str pyogenes* with parenteral penicillin and chloramphenicol in doses that maintained adequate blood-levels for two or three days, they observed no interference, the combination afforded the same degree of protection as penicillin alone In a series of articles, Jones and Finland have attempted to evaluate the activity of two antibiotics in combination by determining the antibacterial activity of the plasma of healthy people at intervals after the drugs had been administered separately or together We have referred to some of their earlier work,[8] [9] and now Finland et al [10] have tested phenoxymethyl penicillin and chloramphenicol in this way Chloramphenicol did not interfere with the action of penicillin against three different gram-positive cocci—a group-A streptococcus, a type-2 pneumococcus, and a *Staph aureus*—nor did it add measurably to the activity of the same dose of penicillin given alone They concluded that the combination has probably no clinical significance

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[1] Winnicott, D W The Child and the Outside World London, 1957

[2] Taylor, S *Lancet*, 1938, i, 759

[3] Jawetz, E , Gunnison J B *J Amer med Ass* 1952, 150, 693

[4] Lepper, M H , Dowling, H F *Arch intern Med* 1951, 88 489

[5] Jawetz, E., Gunnison, J B , Speck, R S , Coleman, V R. *ibid* 1951, 87 349

[6] Ahern, J J , Burnell, J M , Kirby, W M M *Proc Soc exp Biol , N Y* 1952, 79, 568

[7] Speck, R. S , Jawetz, E *Amer J med Sci* 1952, 223, 280

Even if there is no untoward interaction between chloramphenicol and penicillin, it is difficult to envisage a legitimate clinical indication for prescribing these two drugs in combination

ANAPHYLAXIS WITHOUT PREVIOUS SENSITISATION

THOSE who have to administer antitoxin are alive to the danger of anaphylactic shock in patients who may have become sensitised by previous treatment with antitoxin Presumably in sensitised persons antibodies have been produced to serum-proteins present in the earlier dose of antitoxin, and the reaction of these antibodies with the protein in the subsequent dose of antitoxin gives rise to some toxic substance—possibly histamine—which may prove lethal unless adrenaline is administered promptly The relation of anaphylaxis to allergy, the explanation of the toxic effect of the combining of antigen and antibody, and the site of the injury reaction are still mysteries But anaphylactic reactions may be elicited in vitro, for smooth muscle such as strips of uterus or intestine from sensitised animals contracts when it is brought into contact with the specific antigen to which the animal is sensitive [11] Not only does anaphylactic shock occur in animals previously sensitised with the antigen, but so-called " passive anaphylaxis " is observed when administration of antibody from another animal is followed after an interval by administration of the specific antigen. It has been suggested that the time interval before maximum sensitivity to passive anaphylaxis develops may represent the time necessary for fixation of antibody to tissue cells [12]

A reasonable view therefore would be that anaphylactic shock is due to the union of antigen with antibody in or at the surface of tissue cells causing cell injury and leading to the production of a histamine-like toxic substance by the cell On the other hand, acute shock in guineapigs can be elicited by injecting a mixture of antigen and antibody which have already been incubated together in vitro for a short time,[13] so it is not necessary for the antibody to be first anchored to the tissue cells before coming into contact with the specific antigen This type of acute or even fatal reaction after injection of " toxified " serum is sometimes regarded as distinguishable from true anaphylaxis and is described as anaphylactoid shock The severe shock in guineapigs produced by injecting soluble complexes of antigen and precipitating antibody [14] is presumably of this type Recently [15] it has been found that injection into mice of soluble antigen-antibody complexes produces severe shock, the antigens used being bovine serum-albumin and *Hæmophilus pertussis* vaccine In some cases the soluble complexes were prepared by adding an eightfold excess of antigen to the appropriate antibody, and in other experiments equivalent amounts of antigen and antibody were first mixed, and the resulting precipitate was washed and then dissolved by adding a tenfold excess of antigen With the preparation from the washed antigen-antibody precipitate the mortality among the injected mice was lower This suggests that the shock-producing factor may be formed when the antigen and antibody combine in vitro and is removed by washing the precipitate It is perhaps significant that peptone shock produced by protein breakdown products closely resembles anaphylactic and anaphylactoid reactions

IN ARDUIS FIDELIS

BY royal warrant of June 23, 1898, the Army Medical Staff was amalgamated with the Medical Staff Corps to form the Royal Army Medical Corps, and on Tuesday of last week the diamond jubilee of the Corps was celebrated with due magnificence at a service in Westminster Abbey attended by Queen Elizabeth the Queen Mother, colonel-in-chief On the following day the British Medical Association, whose persistent pressure on Governments did so much to bring about the R.A M C 's formation, gathered a large and notable audience in its great hall There they had the rare experience of hearing a commemorative oration delivered by an orator—yet in an unassuming way that made it wholly delightful

Sir Gordon Gordon-Taylor had qualified himself for the occasion first by graduating in classics at Aberdeen in the year when the R.A M C was born, and secondly by his surgical service with the Army in France in the first world war—long before the second transformed him into an admiral Having recalled some of the great but faraway figures of British military medicine, he spoke of the R A M C 's contribution to preventive medicine implied by four of the names carved outside the London School of Hygiene—Parkes, Leishman, Bruce, and Ross Then he turned to the men he knew in France, bringing each to life for a moment by his memories "The whole world is a tomb for heroic men ", and he told us how, the week before, he had paid another visit to Flanders, in the rain so characteristic of that country, and had stood beside the grave of Noel Chavasse, in the cemetery at Brandhoek, which lies exactly where Arthur Martin-Leake had the main dressing-station of his field ambulance These two doctors both received the Victoria Cross twice To the present members of the Corps he said that its great traditions are safe in their hands " Fidelity is, next to courage, the loveliest virtue "

Prof ANDRIJA STAMPAR, a former president of the Assembly of the World Health Organisation, died on June 25 at Zagreb

At their meeting last month the Central Health Services Council re-elected Lord COHEN OF BIRKENHEAD as their chairman.

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[8] *Lancet*, 1957, ii 177
[9] *ibid* p 1207
[10] Finland M Pryles, C V Jones, W F *New Engl J Med* 1958, 258, 817
[11] Dakin H D, Dale, H H *Biochem J* 1919, 13, 248
[12] Kabat, E A., Benacerraf, B *J Immunol* 1949, 62, 97
[13] Friedemann, U *Z ImmunForsch* 1909, 2, 591
[14] Germuth, F G, McKinnon, G E. *Bull Johns Hopk Hosp* 1957, 101, 137
[15] Tokuda, S, Weiser, R S *Science*, 1958, 127, 1237

Special Articles

CASE-WORK IN THE TEACHING OF PSYCHIATRY

T T DAVIES
MEDICAL STUDENT

E T L DAVIES
MEDICAL STUDENT

DESMOND O'NEILL
M C, M D Belf, M R C P, D P M
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WRITING about the fragmentation of knowledge, a distinguished physician and teacher of medicine said

> " I sometimes feel when I listen to these eminent scientists that their arguments are all perfectly valid, except that they have forgotten one thing—that the subject of their improving exercises is a living, feeling, and, we hope, thinking human being Nowadays, be it in medicine, be it in education, be it in political reform, there seems to be a tendency to forget the individual "

This observation of Pickering's (1955) about the medical student applies with even more force to the patient the more advanced the physical methods of diagnosis the greater is the risk that the ill person will get lost in a welter of figures and charts and wave-recordings

We describe here an experiment in the handling of ill and emotionally disturbed people by the student himself, under supervision by a senior We believe that case-work of this kind can help in a practical way to prepare him for dealing with the patients he will meet in his professional life We think it better that he should be exposed to this experience within the framework of a teaching hospital than in the rough and tumble of practice without adequate guidance

In the clinical part of his training the student of medicine learns by observing his seniors at work, by reading, by listening to lectures, and by working with sick people The degree of participation, or involvement, in his work is least when he is passively taking information in, and most when he is actively concerned in what is happening to the patient Methods of teaching that encourage participation, such as the case-seminar with discussion, seem to engage the student's interest and enthusiasm more than the purely didactic methods, though in a balanced course both have their place When patients are entrusted to his care, his attitude undergoes an important change he moves over from being an observer of the art of medicine to being a participant, albeit in a subordinate role

In the teaching of psychiatry two kinds of knowledge have to be imparted (1) the syndromes of mental illness, major and minor, and their diagnosis and treatment, and (2) the understanding and management of a personal relationship between the doctor (or the doctor-in-training) and his patient Case-work, as we use it, contributes a great deal to the second, but it does not take the place of systematic teaching in the first

The ability to take a complete and meaningful history of the patient's illness calls for skill in interviewing, a skill which is of first importance in clinical medicine This ability is one function of an effective doctor-patient relationship, it can be fostered through experience and discussion, and continued contact with the patient is here valuable, for it allows the novice to confirm, refute, or amplify his initial impressions Direct questioning of the patient is not always the best approach The student needs also to learn how to listen, when to comment, and when to keep silent, and how to evaluate what the patient says Some patients require help to express their thoughts, and others ramble so much that a little direction has to be applied Knowledge when to do one of these and when the other takes time to acquire The attitude of the interviewer is important in determining the course of the interview, and with repeated interviews the student comes to see how this influence operates

Method

The first step is that the student who wishes to know more about psychiatry comes to the outpatient clinic on the day when new patients are seen This attendance is voluntary, and thus the students who have taken part in the experiment are a self-selected group One, two, or three students (not more) " sit in " on the consultant's interviews with each patient When the nature and the severity of the illness have been assessed by the consultant, and the patient has left the room, the case is discussed, if it seems suitable for handling by a student, one of those present may be asked whether he would like to take the patient on At this point there is a " feeling-judgment " to be made, if the student feels unduly irritated or antagonised by the patient and his complaints, or unduly attracted, it will be prudent to decline In his later career he will, of course, have to deal with patients of this kind, but it is unwise for him to begin his case-work with one of them If he decides to accept, appointments are made for the patient to attend once a week during clinic hours, when the supervisor (the consultant or his deputy) is available

Patients chosen for case-work fall into two broad classes

(1) Those with anxiety states, or depression, or one of the common stress disorders, such as abdominal discontent These can be helped, and often helped considerably, by regular interviews with ventilation of feeling and the working-through of personal problems

(2) Those with an established illness, such as a paranoid state, which is not progressive Patients in this category attend for observation, the student learns by observing them and reporting back to his supervisor As a rule there is little else to be done, except when some environmental change is called for, this will be decided on after a conference with the social worker

Perhaps from a third to a half of the patients coming to a psychiatric clinic can be assigned to a student Where the illness is too massive or too complicated, or where there are special features which make the case unsuitable (e g, homosexuality with much tension), the patient is dealt with in some other way When the student undertakes to look after a patient he must see to it that his sessions in the clinic are kept free from other duties for a reasonable distance ahead—say two or three months

The student is present on the patients' first attendance at the clinic and is introduced to them as a doctor-in-training he is thus recognised as one of the team The patient selected for case-work is asked whether he will agree to the consultant calling on the student for assistance in the handling of his case, and this agreement is always forthcoming, if the selection has been wise The patient knows that he can always ask to see the consultant, or supervisor, again at any time, it is surprising, and instructive, to see how seldom this request is made

Where the patient is having medication—say, with a sedative drug—and makes an inquiry about this at his interview with the student, he is told that the consultant's advice will be sought before any change is made In general, drug therapy is kept to a minimum, or omitted altogether, during the course of case-work

Supervision

Close supervision of the student's work is an essential part of the plan His session with the patient will last 40–50 minutes, he may make notes at the time or write a summary of the conversation afterwards He then brings his notes directly to the supervisor, and the material of the session is discussed at some length If there is a difficulty the patient may be brought back for a fresh appraisal by the supervisor From the student's interview there will emerge (1) the present state of the patient, and how the illness is progressing, (2) further data about the emotional background of the illness, and (3) the reaction of the student to what the patient says and does, this is especially important

During the supervisory sessions the aims of the departmental team in helping the patient are formulated The tendency of the beginner is to strive for perfection, and to feel frustrated if a perfectly harmonious adjustment cannot be achieved Discussion with the supervisor, and with his fellow-students, promotes a realistic assessment of what can and cannot be done

Some direction by the supervisor of the student's activity will, of course, be necessary this does not consist of a series of orders but rather a working-out by student and senior together of the best and most practicable way of handling each new situation as it arises In the main the student's attitude will be neutral and cautious, he takes care to refrain from taking sides or being drawn into giving advice

Termination of the case-work relationship does not seem to offer special difficulty The rapport between the student and his patient is never allowed to become too intense, so that " weaning " is not attended by depression or a recurrence of illness The patient retains his contact with the clinic and hence does not feel cut off and rejected

Attitude of Student

Naturally at the outset the student is diffident—he is feeling his way At this stage he is advised to say as little as possible, his main task is listening, not talking, and he must strive to adopt a sympathetic, attentive, noncritical attitude which will encourage the patient to unburden himself In the opening phase of his work with patients the student commonly feels mildly guilty He feels that he is " only a student ", and wonders if it is fair for the patient to be seen by him and not by a qualified doctor He soon comes to see, however, that the patient generally benefits from their sessions together, and that his own professional status is less important than the qualities of personality he can bring into the situation His feelings of guilt and inadequacy should be brought out into the open as soon as they appear and freely discussed he can be shown readily enough that he is putting into the patient-relationship at least as much as he is getting out of it

Another common reaction is one of discouragement at the slow rate of progress in the illness—e g , a long-standing anxiety depression From this he begins to learn how to tolerate patients who get better slowly, or perhaps do not progress at all, and that the determining causes of improvement, or lack of improvement, are much more in the patient than in him He learns that every illness, and every human relationship, has its ups and downs, and he takes a more objective view of the downs The student is never given a patient with whom he feels entirely out of sympathy, he is free to refuse the case if the patient is much older than himself, or perhaps too close to him in age, or if he feels that he might get entangled in the patient's problems, or for any similar reason

The possibility of entanglement with the patient is sometimes advanced as an objection to case-work, but in practice it is very rare One of us, who has used and tested out this method of teaching over a number of years, has come across no untoward consequences for the patient or the student (O'Neill 1955) Occasionally the student will become overinterested in or overconcerned with his patient, but with regular and close supervision this can easily be dealt with The student's lack of experience of medicine and of life is in our view offset by the fact that he is, apart from examinations, under much less heavy personal pressure than the overworked general practitioner

Case-work should remain a voluntary activity It would be unwise and profitless to make this part of his teaching obligatory. The student who is keen to learn will ask for it, the others should not be compelled, and, if they were, would learn nothing and perhaps become anxious and resistant

Role of Social Worker

The student who is looking after a patient has access to all the services of the department, and can, if need be, call on the psychiatric social worker to see members of the patient's family, or to advise and help with practical social problems Our practice is that the case is thoroughly discussed by the student, the consultant, and the social worker in conference before the referral is made, in this way the role to be taken by each is defined and understood, and there is no overlapping After the social worker's interview she will discuss her findings with the student or in conference It is a valuable experience for the student to join in a team with workers in other disciplines, he can observe the social worker's approach and learn from her about the importance of family setting, housing conditions, problems of adaptation to a new culture, and the other determinants of illness which are her special province

Objections and Advantages

Some of the risks and objections have been dealt with above One theoretical objection is that the kind of student who is attracted to case-work in psychiatry is likely to be a " neurotic " person seeking therapy for himself On the contrary, the students who apply to have patients of their own include some of the most mature and intelligent of their year

It has been suggested that the medical student may become confused or embarrassed when the patient tries to discuss sexual problems We have not found that this presents any real difficulty, provided that the topics of discussion at the interview are worked through with the supervisor, and the student's own feelings about them are given some outlet A feeling-tone of shame or embarrassment in the interview situation, if it should become noticeable, can be taken up and analysed objectively It goes without saying that sexual conflict is an important contributory cause of the illnesses that bring patients to the clinic, and knowing something of how to deal with these is a valuable asset to the doctor going out into the world

We have students in their first clinical year, and students in their third year, taking part in case-work There is little to choose in degree of competence, or in emotional reaction, between the two The most important differences are not in terms of phase of clinical progress, but in terms of disposition and attitude In terms of benefit to the patient, the first-year men do just as well What seems to count, in the case-work situation, is less a formal knowledge of psychiatry or medicine than qualities of personality and motivation

The main advantage of case-work is that it gives the student more confidence and more insight, and better comprehension of the diversity and complexity of human illness He becomes more receptive to the " undertones " of communication—" reading between the lines ", as a patient once put it He learns, too, about his own reactions to the ill person, and how these can be recognised and tolerated without threatening his relation with the patient He learns how to handle without agitation the patient who is openly hostile, the patient who is unduly demanding, or theatrical, or flirtatious, the patient who seeks to manipulate the staff of the clinic for his own ends In short, he learns how people behave when they are ill and anxious, and how the illness may be utilised for gain

Open Questions

Of course, there are questions about the place of case-work in the teaching of psychiatry which await answers One such is what is the most appropriate place for it in the curriculum—which of the clinical years? What reading, if any, should be done? There is an argument against absorbing much textbook material before embarking on case-work, that it tends to set up in the student's mind preconceptions about what he should find, and that it tends to foster an " intellectualising " of the task, with the result that the student looks for security in lists and rules rather than in his own judgments of feeling

What is the place of the formal lecture? Our experience has been that lectures, when not illustrated by demonstration of a patient, make less impact on the student's mind than seminars, or teaching with the aid of the one-way screen (Millar 1954) As Millar said, " Meaning must be given to the complex by the simple, to the abstract by the concrete, to generalities by particulars, to concepts by percepts "

Illustrative Case-reports

One example of a successful outcome in the handling of a patient with several stress disorders by a student has been published already (Goldman 1955) Other examples are given here

Case 1—An engineering office worker, aged 27, was an anxious man with palpitations, vomiting, spots before eyes, and a dry skin He was seen in the outpatient department over four months (fifteen sessions) The youngest of seven children, he had been reared in Eire and given no instruction about sex His symptoms appeared only when he was alone or visited a cinema or a church During his sessions at the clinic there gradually came to light strong feelings of guilt over masturbation and nocturnal emissions in adolescence, all this time he believed himself to be oversexed He said that he had been worried about this for a long time, and wanted to get it off his chest After the last session he was much less anxious and preoccupied with his symptoms A few months later he was cheerful and confident and had no complaints

Case 2—A secretary, aged 16, complained chiefly of feelings of unreality, depression, and fear of death She had attended the clinic weekly for about three months and was still attending Her parents have never got on well, and she was on bad terms with her father—he is " always finding fault, and enjoys arguments " She cannot resist an argument either She was inclined to blame her father for the scenes, and to minimise her own part in them She has been going out with boys since she was 11 years old and has no other real interests She indulges in very heavy petting but always stops short of intercourse—she becomes very much aroused but gets frightened One aim of discussion during her sessions has been to improve her relations with her father and promote insight into her own behaviour with him She has also come to recognise how excessive erotic stimulation can provoke tension She is now less depressed, and her sleep is much sounder, the unreality feelings are still present, but she is less concerned about them

Other Studies of Case-work in Teaching

Houston and Allen (1957) describe a clinical programme for second-year students in the department of psychiatry of the University of California

Each student is assigned one psychiatric patient with whom he works voluntarily in his own time in the outpatient department The patient is seen in weekly one-hour interviews through most of the academic year Supervisors are drawn from residents, fellows, and junior psychiatrists, one of these devotes an hour to the student each week " Orientation meetings " are held to discuss the various questions which emerge from the students' work with patients Houston and Allen comment that the supervisors were often surprised at how well the student had done, and felt humble on comparing the student's performance in the doctor-patient relationship with that of a novice clinician in any field

Coleman (1951) says " The objective of psychiatric teaching is to turn out better doctors, not better psychiatrists "

In his department in the University of Colorado two students work as a team in the pædiatric outpatient clinic, one student seeing the mother, and the other the child The interviews are then fully discussed with the psychiatrist The student, as Coleman says, learns to use his own personality resources He believes that it is much easier to teach medical students than graduate residents; the attitudes of the qualified doctor towards the handling of the disturbed patient are already becoming fixed, whereas the attitudes of the student are still being formed

Comments

Balint (1957) said " Illness is a fruitless struggle by the patient to resolve his conflicts, therapy is an attempt by the doctor to intervene in this dynamic process so that a better equilibrium can be attained " The knowledge which the student must acquire if he is to become a fully effective doctor Balint has named " the pathology of the whole person " In this new pathology there must be, as he says, a long chapter devoted to the most important therapeutic agent, the relationship between the patient and his doctor We consider that case-work by the student will give him insight into this all-important relationship that is unlikely to come by reading and observation alone

Preparation of the student for dealing with disorders of emotional origin is of particular importance for those who intend to work in urban communities Finlay et al (1954) estimated that in an urban practice one patient in five who call upon the doctor does so because of a stress disorder

The attitude of the public in general, and of medical students, towards the psychological aspect of illness is changing Suspicion and ridicule are giving place to curiosity, active interest, and a willingness to devote time and trouble to study and work in this field The student is under some handicap when he first comes to deal with patients during his training His natural and human approach to the sick person tends to become overlaid by the attitudes which preclinical teaching may beget—especially an overvaluation of the physical aspects of causation of disease Case-work brings him back into full contact with his chief object of study—the person who is ill It helps him to place the biophysics and biochemistry of medicine in proper perspective

Summary

One method of teaching in psychiatry is the handling of ill and emotionally disturbed people by the medical student himself under supervision

Its advantages and possible hazards are appraised

It offers the student an opportunity for gaining confidence, and insight into the meaning of illness, that may not be so readily acquired in other ways

We are indebted to Prof W S Peart for his interest and help in the preparation of this paper, and to Miss Dorothy Asbury for her contribution to discussions

REFERENCES

Balint, M (1957) *Lancet*, ii, 1015
Coleman, J (1951) *J med Educ* 26, 2
Finlay, B , et al (1954) *Practitioner*, 172, 183
Goldman, K (1955) *St Mary's Hosp Gaz* 61, 111
Houston, M , Allen, D W (1957) *J med Educ* 32, 483
Millar, W M (1954) *Brit J med Psychol* 27, 30
O Neill, D (1955) Modern Trends in Psychomatic Medicine, p 56 London
Pickering G (1955) *Lancet*, ii, 1149

SENIOR REGISTRARS

THE Ministry of Health has outlined arrangements[1] for the selection of some posts without limit of tenure for senior registrars who have finished their training and have not yet obtained higher appointments[2]

Hospital authorities are asked to submit proposals for designating some senior-registrar posts which will provide responsible work commensurate with that normally expected of a fourth-year senior registrar, and which are within the present total of senior registrars The new posts " must not be regarded as a substitute for additional consultant posts ", and the senior registrars selected will be free to continue to compete for higher appointments

> " In the course of their review of senior registrar posts, Boards may well find that there are posts held by time expired senior registrars which should be held by part-time or whole-time consultants Such findings should be reported with the proposals in respect of special posts "

The Minister will be advised on the proposals by the professional committee which advises him on consultant appointments The future use of posts of this type will depend on the outcome of the study by the working party on medical staffing structure in the hospital service[2]

In filling posts whose designation is approved by the Minister, boards should consider applications only from senior registrars who have completed their four years of training The posts should be advertised, except where the board, after taking account of the advice of its medical advisory committee, is satisfied that the present occupant of the post is the best candidate that would be likely to come forward if the post were advertised Appointments will be of unspecified duration, but the need for the continued existence of a post will be open to review when it falls vacant Remuneration is to be announced later

Before Our Time

THE AUTOBIOGRAPHY OF CHARLES DARWIN *

Charles Darwin's autobiography is a true testament of science, and, although it contains cautionary elements for those endowed with genius and a passion for discovery, it is nevertheless inspiring reading for the young scientist It is a plain record of the life and work of a man who ranks with Newton as the most important of English scientists Charles Darwin told the truth about himself as he saw it, as all diarists and autobiographers must if they wish their records to endure

James Boswell told the whole truth about himself, shamelessly and tediously, because anything that happened to him, James Boswell, was important and worthy of record " Jamie, Jamie," said his father, Lord Auchinleck, sadly, " if ye sullied your breeches ye'd tell the world " Edward Gibbon told the truth about himself (perhaps not the whole truth) because this was the lifelong habit of the historian Charles Darwin had a still higher standard of accurate reporting, for his training, unlike the historian's, was to record the facts elicited by personal observation and experiment

The interest of the subject and the accuracy of the record give it a high place among English autobiographies Although there is in his prose no rhythm and no eloquence, the plain style well matches the simple story He records the ordinary happenings of any man's life with a simplicity which amounts to naiveté For example, of his life in Cambridge as an undergraduate he wrote

> " We sometimes drank too much, with jolly singing and playing cards afterwards I know that I ought to feel ashamed of days and evenings thus spent, but as some of my friends were very pleasant and we were all in the highest spirits I cannot help looking back to these times with much pleasure "

Charles Darwin had no insight into his own personality or into the nature of his chronic invalidism, but his story is told so frankly and so ingenuously that the instructed reader can today learn more of Charles Darwin than he knew of himself

The autobiography was written for his family in 1876, but since it was written at the instance of a German editor, even the modest Charles must have expected that it would one day be published, as indeed it was five years after his death, in the *Life and Letters of Charles Darwin*, edited by his son, Sir Francis Darwin Some passages were then omitted either because they were too harsh in their criticism of individuals, or too frank in their statement of Darwin's views on religion The autobiography was republished here in 1929 and again in America in 1950, but it has not recently been readily available in this country, and although the personality and work of Charles Darwin have been given great attention in the past twenty years, the autobiography has not been widely read.

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[1] H.M (58) 58
[2] See *Lancet*, 1957, i, 906

* The Autobiography of Charles Darwin Edited by his granddaughter NORA BARLOW London Collins 1958 Pp 253 16s

Lady Barlow has then done well to give us a full and accurate transcript of the manuscript which is now in the Cambridge University Library. The restored passages contain nearly 10,000 words and, although they neither enlarge nor correct for us the portrait of Charles Darwin, it is highly satisfactory to have at last the complete text.

It is to be hoped that this reprint, together with the chapter written by Sir Francis Darwin concerning his father's personality and method of work, will soon find a place in one of the cheap editions of the classics. This is the first time, I think, that the Autobiography has been published without the complementary reminiscences of his son, and the loss is great.

This omission must have been the result of considered editorial policy, but it clearly demonstrates that Charles related only half the tale and Francis, with the skill of an artist tempered by the affection of a devoted son, told the rest. In partial compensation we are given several appendices covering 100 pages, including an essay on Charles' attitude to his grandfather, Dr Erasmus Darwin, and another on his controversy with Samuel Butler.

* * *

The outline of the story told in the Autobiography is well known, even by those who have not read it. In it Darwin describes the slow growth of his scientific passion, before he joined the *Beagle* on her five-year voyage his geological studies had begun, but of this time he writes "I should have thought myself mad to give up the first days of partridge-shooting for geology or any other science." After his return to England and his marriage to Emma Wedgwood his research gradually excluded all other interests, except his love for his wife and children. Social life, shooting, literature, music, the meeting of scientific societies, the cultivation of friendship—all these were excluded as the formulation and proof of the great hypotheses increasingly filled his mind. The night brought no escape, with its reiteration of the doings of the day and its plans for the morrow, but relief by day was provided by the newspaper, which he read for himself, and by novels which were read to him each day for an hour and a half by the devoted Emma, who also accompanied him each evening in two games of backgammon. When I wrote in *The Lancet* in 1943 that "four hours' work in the daytime sufficed for the performance of the most important scientific work of the nineteenth century", Sir Arthur Keith wrote to me pointing out that "Darwin's brain was a broody fowl—always sitting on a brood—a 24 hour day, not 4 hours!"

Inherited wealth and chronic ill health were the begetters of this situation so fortunate for science, a situation impossible either for the children of the poor or for the healthy—at least if they carry the burden of guilt which afflicted the sensitive conscience of Charles Darwin. The shawl, which was usually draped over his shoulders, became both for him and his children the badge of invalidism—a distress signal to which the family gave unquestioning and ready response. And the cause of his illness? An autonomic disorder, bred, like other autonomic disorders, by Constitution out of Environment, conceived and nourished by the guilt which resulted from his suppressed hostility to that godlike being his father—all-wise, all-kind, omniscient and omnipotent.

* * *

It was a curious fate that brought this prototype father-idolater into conflict with that prototype father-hater, Samuel Butler. The aggressive expression of Samuel's hatred of Canon Butler did not mitigate his violence towards any other father-figure who treated him with contempt, and Charles' unawareness of his hostility to his own father did not reduce his sensitivity to criticism nor diminish a guilty son's need for consolation and security when attacked. Charles had been at school at Shrewsbury with Samuel's father and an undergraduate with him at Cambridge. Samuel was more than an acquaintance, he had also been a professed admirer of Darwin's scientific work, and it was not until 1877 with the publication of *Life and Habit* that he became openly critical of Darwinism. Charles disdained an adversary whose arguments were not founded on scientific fact, but he could not understand, as he wrote to Huxley, why Butler was "so bitter against" him. How could he know, or indeed care, that he had become an offending father-figure for a rebellious son?

The quarrel arose after the publication in 1879 of Charles' *Life of Erasmus Darwin*, which contained a translation of an essay by Ernest Krause which had originally appeared in the German scientific journal, *Kosmos*. While the book was in preparation Charles sent Krause a copy of Samuel Butler's *Evolution Old and New*, which had just been published, with the hope "that he would not expend much powder and shot on Mr Butler as he really is not worthy of it. His work is merely ephemeral." Krause revised his article and included critical references to the views of Butler, although not mentioning him by name. When the *Life of Erasmus Darwin* was published there was no indication that the original article had been revised or by whom and, worse still, there was a footnote in the preface stating that Mr Butler's book *Evolution Old and New* had appeared since Dr Krause's article was published. Butler asked Darwin for an explanation, Darwin replied that "this is so common a practice that it never occurred to me to state that the article had been modified." Butler, unsatisfied, stated his grievance in a letter to the *Athenæum*. Darwin then remembered what he had forgotten, that he had indeed written a paragraph for inclusion in his book stating that Krause had revised this article, remembered then, too, that at Krause's instance, he had caused this paragraph to be omitted, and perhaps did not recognise, even then, that his footnote to the preface would justify a charge of duplicity by the inflammable Butler.

Comfort in this assault by the unspeakable Butler was provided by the family in no ordinary degree. As Lady Barlow relates, "the exchange of letters to and from Down, some of which were sent to London by road in the Down carriage, with John the coachman waiting to bring back the answers shows how serious was the flutter in the Darwin Dove-cot." Should Charles admit his error and rebut the charge of duplicity or should he ignore contemptuously the "nearly insane" ravings of a scribbler? He was persuaded by the majority of his family and by his powerful friends (Huxley and Leslie Stephen) not to sally forth from his ivory tower, but some of his sons, including the wise and unimpassioned Francis, gave him better advice which was unfortunately rejected. So Butler's resentment smouldered on in his aggressive breast, and although the fires were temporarily damped down by Darwin's death, he himself was to die unaware of the truth.

If these lapses of memory were examples of the provocative art of forgetting, yet another example of Charles curious forgetfulness is given by Lady Barlow. Charles in his autobiography gave the year of his father's death as 1847, it was in fact 1848.

* * *

The edition of the autobiography published in 1929 in the Thinker's Library omitted the pages relating to Robert Waring Darwin, Charles' father. This long studied experimentally by Poiseuille in the 1830s He described experiments with two types of viscometer for studies of apparent viscosity and of adherence The results depended on the nature of the surfaces, the temperature, the rates of shear, and other conditions Since viscosity studies have been made in the past in glass tubes, his findings, especially on fibrin-coated tubes, appear of particular interest According to his concept blood-vessels have a fine porous endoendothelial lining of fibrin, probably a calcium fibrinate, which is produced and maintained continuously throughout life The existence of an immobile or-nearly immobile layer would insure that micro-coagulation processes, such as fibrin deposition and fibrinolysis, as well as other reactions could take place undisturbed on the vessel wall The widely divergent results from blood systems in contact with various surfaces emphasise the importance of knowledge of the nature of the inner lining of blood-vessels *The formation of an immobile layer along the wall of the tube* through which the material is flowing, " wall adherence," has not hitherto been studied with blood systems This adherent layer, may be compared with the immobile portion of the marginal plasmatic zone in the living blood-vessel postulated by Poiseuille From his studies on apparent viscosity and wall adherence, Dr Copley concluded that the proposed endo-endothelial fibrin film may play a part in regulating the width of the immobile layer and constitute a major factor in aiding circulation by increasing the velocity of blood-flow

Dr P H Staple (Medical Research Laboratories, Charing Cross Hospital) presented a paper jointly with Dr A L Copley on biomicroscopic observations of the plasmatic zone in the capillary beds of frogs and Syrian and Chinese hamsters These workers have developed a new method for producing graded variations in the velocity of blood-flow in small vessels This method enabled many of Poiseuille's observations to be confirmed for the first time Furthermore, by the injection of graphite suspensions or of a dye, they were able to establish in the capillary bed of the Chinese hamster's cheek pouch the existence of an immobile layer in contact with the vessel wall as predicted by Poiseuille for blood flowing in vivo

Dr G W Scott Blair opened the discussion on the rheological interpretations of the foregoing papers He discussed the meaning to be attached to the term " viscosity " in blood systems He saw no objection to defining viscosity as shear stress divided by rate of shear, even when this ratio is not constant, provided that this fact is specifically stated

Prof K Weissenberg (Cambridge), a rheologist, discussed the many possible kinds of turbulence and of dilatancy, both of which phenomena have been observed in flowing blood He also stressed the very large number of possible anomalies of flow

Other speakers pointed out that the presence of adherent layers found behind a column flowing down a tilted tube do not necessarily prove the existence of such layers in full tubes In reply, Dr Copley pointed out that the in-vivo evidence was, in itself, conclusive

Prof M H Knisely (Charleston, U S A.) read a paper on observations of the settling of blood-cell masses to the lower sides of vessels of animals and men during pathologic conditions, which was illustrated by a colour motion picture, taken through a horizontally aimed microscope This most fascinating film showed clearly that there was a pronounced gravitational settlement of red cells in vivo, so that of two vertically disposed branches of a vessel the upper might contain pure plasma while the lower was choked by a mass of cells This novel observation, which demands further study, has important pathological implications Professor Knisely claimed that in some cases it seemed most probable that blood-cell masses settle in great numbers and become stationary long before the death of the subject, which they help to cause

In closing the meeting, the Chairman said that he was delighted that so many participants from all over the country and some from abroad had attended He expressed the hope that further meetings on hæmorheology would be organised in other centres

The rheological aspects of the conference are to be reported in *Nature*

In England Now

A Running Commentary by Peripatetic Correspondents

Well, it's all over at last and we're back to normal There were those of us, mind you, that actually enjoyed the bus strike, and we're a bit sad to have these great red bloated monsters edging us over the white line as in days of yore No longer can we pull up our saloon at bus stops and see it filled delightfully with typists, models, apprentice actresses, or, earlier in the day, charwomen, keeping a score of Cars They Have Ridden In, who proudly told us of the Rolls with chauffeur that took no less than 12 of them right into the City My holiest load was a Sister of Mercy hotfoot with Inj Streptomycin, who packed her voluminous robes into the front seat and, for some inexplicable reason, a small roll of lino in the back (for some ceremonial purpose ?) Such was her aura of sanctity that I found myself three miles off my road at her destination without quite realising it but she did invite me back to her mission for coffee Now the strike is over, to offer a lift, though in all Christian charity, might be interpreted as carrying a dark nefarious purpose folk that last week wrestled with each other to squeeze in at my rear door would now fly screaming and dial 999

I'm afraid of these buses now, too Will the animosity towards private lift-givers, built up over the weeks, lead some irascible busman to ram his livid half-inch armour-plated giant into my frail craft ? Perhaps I should buy a pair of spectacles and try to look like Mr Cousins And another thing—I've lost a good excuse for being late It's a peculiarity of mine that my " psychostat " is set just five minutes after everyone else's, which means stumbling over knees at lectures and creeping silently into ward rounds behind the treatment trolley With the magic words " No bus " all was forgiven, if they knew I had a car the password was " shocking jam " Now I've got to fall back on sand in the carburettor and the kids being ill

But, then, I must stop thinking hard thoughts about the busmen, bless them, after all, don't *I* have a pay dispute coming up any day now ?

* * *

I had been admitted for what is euphemistically called a minor operation, and I could not have been better looked after The surgeon was skilful, attentive, and kind, Sister was charming, her nurses highly decorative

The little staff nurse was particularly sweet, but we had a few moments of difficulty when she brought me my first meal in hospital, it was the usual assortment of meat and vegetables and I was just about to start when she returned, in some confusion " I'm sorry," she said, " but I'm afraid I shall have to take that away again, you're not supposed to be eating it—after all, you are a hæmorrhoid, aren't you ? "

Thus, in later years, do we flinch once again under the terms of abuse of our student days, time alters many things but, clearly, to the perceptive observer, character—despite added weight and dignity—does not change

* * *

Queueing for the gallery to see the Moscow Arts Theatre was an entertainment in itself A pleasant, moderately shabby man who joined the queue just behind us started a conversation at once, as though we were old friends We kept our end up pretty well for a time, but quickly got out of our depth as it became evident that he spent every evening of the week in queues and had seen everything in London worth mentioning, as soon as it opened, for several years back I wondered how he earned his living, teaching in a progressive school, perhaps, or could he be a " resting " actor ? Two hardbitten, theatrically orientated women behind him entered the discussion uninvited and completed our annihilation Respectable middle-aged women in correct hats, with the calmly patient expressions of housewives inured to queueing, rubbed shoulders with flighty young creatures who darted out of line at intervals to chatter

Personal Papers

THE VISITING-LIST

As others have done before, our medical dining-club at its February meeting discussed the future of general practice We all have views on this (we are an enlightened lot), but perhaps it's a bit late in the day to expect any very novel opinions on this familiar subject What did startle us was a small collection of *facts* which came out almost accidentally near the end After we'd been talking for some time about what practitioners do, and what they ought to do, someone turned to the family doctor who'd opened the proceedings and said "Tell us what *you* did today What kind of patients did you see?" So he produced his visiting-list, and it surprised us Since it may surprise others, I asked him for a copy of it, with his remarks as he gave them to us Here it is

1 *Varicose ulcer* in a filthy man over 70 No hope of improving the dirty house

2 *Acute bronchitis*—Woman of 74 Lives alone, dependent on neighbours One hour's domestic help daily

3 *Aortic regurgitation*—Man over 70 Arteriosclerosis

4 *Cerebral thrombosis*—Man over 80, nursed by wife also over 80

5 *Furuncle of ear*—Woman in great pain and distress

6 *Carcinoma of vulva*—Recurrence after removal of vulva

7 *Acute bronchitis* in a middle-aged man with pulmonary tuberculosis

8 *Tonsillitis* in a child

9 *Mumps* in a middle-aged woman

10 *Influenza* in a young man

11 *Hæmatemesis* in an imbecile Uncooperative young man, with spastic diplegia, treated at home

12 *Lumbago* in an Army officer To be X-rayed (?) disc lesion

13 *Loss of voice* in a schoolgirl Probably simple laryngitis, to be referred to E N T specialist if no improvement in two weeks

14 *Root pain from osteoporosis* in a woman over 80

15 *Hæmorrhage* in a young pregnant woman Admitted to hospital with premature labour

16 *Gangrene of finger* following crush injury Woman over 80

17 *Acute bronchiolitis* in two children.

18 *Acute bronchiolitis* in a child

19 *Acute bronchiolitis* in a child

20 *Secondary carcinoma of liver*—Resection of rectum three years ago Ascites and œdema of feet Difficult case to manage

21 *Acute bronchiolitis* in a child

22 *Cardiac failure* in a man of 79 looked after by his wife, herself a certifiable melancholic

23 *Pain*, from defective peripheral circulation, in a man of 79

24 *Antenatal examination*

25 *Incarcerated hernia* in a woman over 80 with senile confusion Reduction

26 *Rheumatoid arthritis*—This woman also has auricular fibrillation

27 *Sore throat*—A schoolgirl with pharyngitis

28 *Hypertension and chronic bronchitis* in a middle-aged man

29 *Diphtheria immunisation*—Child's mother could not bring him to surgery

30 *Cut hand*—Man of 87 fell and cut his hand Five stitches

31 *Acute bronchiolitis* in a child

32 *Gastroenteritis* in a baby—12 miles from the surgery

33 *Laryngitis* in a woman

Unusually heavy? About average, he said, for the time of year—there are four doctors in the practice, with about 9000 National Health Service patients and three appointments a garrison, a prison, and a factory February saw the tail of an outbreak of bronchiolitis in young children, which accounts for 6 of those on the list

But of course what is chiefly striking about these patients is that so many of them were old, that so many of them were gravely ill (having passed beyond hope of hospital cure), and that almost all were treated at home—the only one admitted to hospital being the young woman in premature labour, who had already been booked Thanks to consultant opinions and the practitioners' own free access to pathology and X-rays, there was a diagnosis in every case, and this must sometimes have reduced the need for admission

I have never thought it true that the practitioner in this country is forced by circumstances into becoming no more than a clerk and certificator, and now I shall be rather more sceptical when people tell me that general practice concerns itself only with minor illness You too perhaps?

F

Congresses

FLOW OF BLOOD IN RELATION TO VESSEL WALL

A MEETING, sponsored by the clinical research committee of Charing Cross Hospital, to discuss the flow of blood in relation to the vessel wall, was held on June 13 at the Charing Cross Hospital Medical School

Opening the conference, Mr N C LAKE, the chairman, said that it was the first ever devoted exclusively to hæmorheology Although any addition to medical jargon was to be deplored the title "hæmorheology" was justified, for the subject was a vast one of rapidly increasing importance (Hæmorheology is a term introduced by Copley[1] and defined as covering "the deformation and flow—i e, rheological—properties of cellular and plasmatic components of blood in macroscopic, microscopic and sub-microscopic dimensions and the rheological properties of vessel structure with which blood comes in direct contact") Extensions in cardiac and vascular surgery had raised fresh questions which demanded an answer, and the growing incidence of cerebral and cardiac vascular lesions presented new problems for the physicians He then gave examples of the ways in which rheological studies might aid the clinician in his practical work, finally quoting from the preface to James Parkinson's *Essay on the Shaking Palsy* (1817) "That these friends to humanity and medical science, who have already unveiled to us many of the morbid processes by which health and life is abridged, might be excited to extend their researches to this malady, is much to be desired "—a mandate to all research-workers

Dr G W SCOTT BLAIR (Reading), a rheologist, surveyed work on the flow of suspensions through tubes with special reference to blood He pointed out that during the past thirty years two groups of workers have been studying certain deviations from Poiseuille's law of flow almost completely independently of each other Particularly Fahræus and his school in Sweden have worked on blood, whereas many rheologists in quite other fields (e g, paints, clays, plastics) have pursued independent investigations with no knowledge of blood Only recently have the two lines of investigation converged, with much mutual benefit

Dr A L COPLEY (Medical Research Laboratories, Charing Cross Hospital) reported on studies of adherence and viscosity of blood, plasma, and serum in contact with surfaces foreign to blood and with fibrin surfaces His investigations were based on the observations of the plasmatic zone in the living blood-vessel, already known to Malpighi in the 17th century but

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[1] Copley, A L *J Colloid Sci* 1952, 7, 323

Weary—I think it will be appreciated that these people are putting an abnormal strain on their bodily functions during pregnancy By typifying these women in the film, it is hoped that the expectant mothers will, by their cooperation with their medical advisers, remove these factors of overweight, anæmia, malnutrition, and fatigue which hasten the onset of toxæmia in susceptible subjects

I speak as a practical obstetrician dealing more with people than with statistics and theories, and also as obstetric adviser to the film in question I believe that there is very little substance in Professor Platt's criticism, when related to the purpose of the film For one who is an ardent follower of scientific truth, it is strange that Professor Platt should criticise a film which he has never seen, and of which he has read only a brief account Nevertheless, I look forward to spending a pleasant half-hour with him, showing him the film, and providing some relevant references

Kent and Canterbury Hospital,
Canterbury
JEAN R C BURTON-BROWN

ACQUIRED OSTEOGENESIS IMPERFECTA ?

SIR,—Dr. Koumans in his letter last week says that his case of osteogenesis imperfecta had a total blood-protein of 6 8 mg per 100 ml, improving later to 7 2 mg per 100 ml The best people have values of about a thousand times this amount That is the worst of this infernal decimal system Who was it that called it " those damned dots ! " ?

London, N W 3
J W. SHACKLE

GRAVITATIONAL LEG ULCERS IN THE ELDERLY

SIR,—Dr Rivlin is to be congratulated on his very practical article last week. He rightly stresses the importance of the history, for we often depend on this to determine whether the ulcer is varicose or post-thrombotic As he points out, the distinction is useful as it affects treatment and prognosis

Dr Rivlin classified 75% of his series of 200 patients as having varicose ulcers and 15% as post-thrombotic The proportion of varicose ulcers is greater than that found by many workers in recent years, and one wonders whether the name of his clinic attracts a larger number with varicose veins than does a general-hospital clinic dealing primarily with leg ulcers Certainly in my own series the proportions are very different. Of 1676 patients with " venous " leg ulcers (i e, excluding those resulting from arthritis, arterial disease, or other conditions) 1172 (69 9%) gave a clear history of thrombophlebitis of the lower limb with much œdema The thrombophlebitis had been associated with various conditions—post-partum 283, injury to the leg 282, unknown causes 154, medical illness 94, fractured leg 79, ante-partum 70, treatment of varicose veins (usually injections) 70, operation (not on the leg) 61, infection of the leg 37, burns of the leg 27, operation on the leg 15 There were in addition 266 patients with no definite history but whose ulcers were probably post-thrombotic.

It would have been interesting to have had Dr Rivlin's views on arterial factors, especially in the 93 patients over the age of 60 There seems little doubt that arteriosclerosis or hypertension or both may play an important part in the ætiology of gravitational ulcers

I have not calculated the statistical significance of Dr Rivlin's figures showing the results of treatment, but wonder whether there is any significant difference between the varicose and post-thrombotic groups A factor of great importance in the rate of healing is the chronicity of the ulceration before treatment is started

Leeds
S T ANNING

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—Your correspondents Mr Bonnin (June 28), Mr Hendry (June 21), and Mr MacKenzie (June 21) are satisfied that the phenomena we attribute to disorders of the disc can be fully explained by mechanical injuries superimposed on the process of desiccation in disc degeneration They find it unnecessary to invoke any other mechanism such as I have postulated in a transient phase of raised internal disc tension It is easy to explain chronic backache by disc desiccation and to explain some attacks of lumbago and sciatica by analogy with the displacement of a torn meniscus in the knee, but there are other aspects which seem to me to demand a more subtle explanation.

Compare, for instance, the quality of the pain of lumbago with the quality of the pain when a patient displaces a cartilage in the knee After the first twenty-four hours a " locked " knee ceases to cause spontaneous pain and is painful only if the patient fails to rest the limb By contrast a severe attack of lumbago will cause spontaneous agony for two or three weeks and resist bed rest and even injections of morphine This persistent spontaneous pain is unlike the response of the body to a simple mechanical displacement, because skeletal tissues rapidly adapt to a displaced fragment and pain will disappear though it will return if function is demanded of the part. It seems to me that the persistent agony of a severe attack of lumbago is more like the pain caused by raised tension inside cavities which resist distension. An alveolar abscess or a boil in the external auditory meatus causes pain which persists in a way which could not be imitated by inserting a solid object of the same shape and size as the bead of pus, because the tissues which were stretched by the solid object would adapt themselves and only a fluid mechanism capable of continued expansion could maintain the tension and so maintain the pain One of the most painful complications in orthopædic surgery is a postoperative hæmarthrosis after meniscectomy, if bleeding from a small artery fills the closed cavity of the knee-joint with blood under tension the postoperative pain is so severe that no amount of morphine will render the patient completely comfortable nor will any position of the limb afford relief, and this condition will persist until the tension is relieved

One of the most surprising things about acute lumbago is that the amount of pain does not seem to be proportional to the amount of organic change visible in the disc. It is possible for a patient to have a violent attack of lumbago in early adult life and thereafter to have attacks for twenty years without the vertebral bodies adjacent to the disc showing any of the changes we associate with degeneration of the annulus, loss of elasticity, or failure of the hydraulic mechanics of the disc. I find it difficult to explain how a young man can quickly recover athletic perfection after a prostrating attack of acute lumbago if the process is merely a degeneration of the annulus leaving this structure capable of rupture by forces which would not damage a normal disc. Would not a young athlete with a degenerate annulus be permanently debarred from sport ?

Like a number of other surgeons ten or twelve years ago I used to explore cases of acute lumbago on the theory that these were caused by protrusions which had emerged in positions such as the midline where a nerve-root was not directly involved to give the picture which otherwise would be sciatica We rarely found convincing protrusions in these cases, but what is cogent to the present argument is that the material removed appeared more often to be normal than to be fibrous and stringy

I agree with the comment in your annotation of June 7 that one of the difficulties in accepting the hypothesis of raised disc tension is that I have never observed swollen and gelatinous disc tissue at operation I do not think that this is an insuperable obstacle to the theory, because the disc is contained inside a tough casing and the pressure can rise isometrically, without the volume increasing very much In my experiments using the cadaveric disc the gaily to friends up or down the queue One of the latter, her bare feet thrust into sandals consisting of a strip of white leather attached precariously to a sole, had toenails painted startling white to match her skirt Young couples in grubby jeans and shapeless sweaters, the girls mostly without make-up and with hair uncombed, stood seriously waiting, sometimes reading, or eating sandwiches out of battered, grimy shopping bags Arty girls in clean, brightly-coloured sailcloth trousers, wearing dazzling make-up and exotic hair-styles, eyed with faint contempt the nice young teachers dressed in flowered summer frocks and engaged in earnest, clear-voiced conversation A tweedy man who was reading the play of the evening in Russian discoursed on it in a voice unmistakably English to his companion, who was also English and tweedy The sound of elderly foreign voices recalling the Moscow Arts Theatre of many years ago mingled with the bored tones of slightly supercilious bowler-hatted youths talking about nothing in particular Soon small boys from nearby flats casually took up positions near the queuers who happened to be eating, and occasionally turned cartwheels or terrorised each other in the intervals when they were not hopefully rushing to open the doors of taxis arriving at the stalls entrance An air of expectancy was heightened by the cheerful, bent little man selling souvenir programmes with a maximum of sales-talk

We did not see any obvious doctors in the queue I wonder what we looked like ourselves?

* * *

In our hospital N A D, I D K, M S U, and other concise contractions help us in the labour of form-filling Now I've met the giant of abbreviations, acromegalic and ponderous in its proportions The X-ray request card simply read as follows "F H N H I U D ?" What *could* it mean? "Frightened hectic nurse has injured upper denture?" No "Fœtal heart not heard Intra-uterine death?"

* * *

A youngish woman came to me about a compensation claim She had given up work as a waitress some months ago and had just been taken on in a new job, for which she was to receive a course of special training which would last for one week She would then become a cosmetic consultant Evidently there are no registrar problems in the beauty parlours

* * *

GAY NIGHT IN A G P's LIFE

11 P M —Receive request to visit Mrs J in her home

11 30 P M —Visited Mrs J, who has lately arrived from West Indies Diagnosed acute appendicitis and advised removal to hospital and made necessary arrangements with E B S

MIDNIGHT —Went to bed

1 50 A M —E B S rang to say they had been advised by ambulance team that mother refused to go to hospital unless her baby went with her and they believed the baby to be only 3 weeks old I advised E B S that baby was nearly 4 months old and could safely be left at home

2 A.M —E B S rang again to say that hospital would not admit the baby I asked them to try other hospitals

2 15 A M —E B S rang again and asked me to call again at patient's house to sort things out.

2 25 A M —Arrive at patient's house again Baby was 15 weeks old, but apparently there was no-one left at home during day to look after it. I drove to local hospital but could not persuade them to alter their minds about admitting baby Returned home, rang another hospital who agreed to admit mother and baby I advised E B S of this and I returned to bed

4 15 A.M —Hospital rang to advise me that Mrs J had taken her discharge almost immediately after admission as (*a*) she felt better, and (*b*) an immediate operation was not to be performed I took no further action

6 30 A M —Night bell rang At front door was Mrs J's husband He told me his wife was much worse and in great pain Would I arrange readmittance to hospital This I did

9 A.M —Start day's work.

Letters to the Editor

N H S. STAFF COLLEGE

SIR,—No amount of legislation or official exhortation can of itself bring together in harmony the three parts of our Health Service

The fullest personal exchange of views at all levels would produce results beneficial to the family doctor, the hospital staff, and the medical officer of health, and through them to the patient

Both industry and many of the leading professions find it advisable to establish central training and liaison units There are staff colleges for the four Defence Services, for bankers, Civil Servants, hospital administrators, and even for trade unionists

Is it not now time to set up a National Health Service Staff College where every sort of problem could be examined dispassionately? Not only the formal aspect of the work but also the private discussions which follow give value to this form of conjoined study

Health Department,
Brighton

W S PARKER
Medical Officer of Health

TIME AND THE NURSE

SIR,—Last year you said "If hospitals were to make it the rule that temperature, pulse-rate, and respiration-rate were to be recorded only if specifically requested by the clinician, nurses would have more time for more important techniques, and their proper work of nursing the sick"[1] When a "hospital" makes a "rule" of this sort, who is the "hospital"? I have been told that in some hospitals your practical suggestion is difficult to put into effect because the medical committees are reluctant to agree to it

Although your suggestion would save much time, its implementation would probably be made easier if it could be demonstrated, in a manner acceptable to medical and to nursing committees alike, not only that routine temperature, pulse-rate, and respiration-rate recordings are of little value but also that the dropping of them is, as you imply, to the advantage of patients as well as nurses No real nurse would wish to save time in this way if the patient were to suffer

Secondly, there are legal considerations would the abolition of this routine mean that the ward-sister must accept legal responsibility for failing to take the recordings exceptionally on her own initiative? If so, routine might prove a cheap form of insurance

Thirdly, what would be the effect on the patient public? Maybe many feel that this routine procedure provides an important opportunity for regular personal contact between patient and nurse, what other regular opportunities are envisaged in the "proper work of nursing the sick" to which you refer?

An important time-saving suggestion of this nature merits thorough investigation

Department of Health Education,
Battersea College of Technology,
London, S W 11

M H OUSELEY

TOXÆMIA IN PREGNANCY

SIR,—I have read Professor Platt's criticism (June 14) of the account (June 7, p 1235) of the new film on this subject In quoting one part of your account he has failed to appreciate what is clearly stated in another part—that the film was made expressly for the education of expectant mothers, and, I might add, not for members of the medical profession

In illustrating the various types of women which he mentions—namely, Mrs Stout, Mrs Pale, and Mrs

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[1] *Lancet*, 1957, ii, 1103

Weary—I think it will be appreciated that these people are putting an abnormal strain on their bodily functions during pregnancy By typifying these women in the film, it is hoped that the expectant mothers will, by their cooperation with their medical advisers, remove these factors of overweight, anæmia, malnutrition, and fatigue which hasten the onset of toxæmia in susceptible subjects

I speak as a practical obstetrician dealing more with people than with statistics and theories, and also as obstetric adviser to the film in question I believe that there is very little substance in Professor Platt's criticism, when related to the purpose of the film For one who is an ardent follower of scientific truth, it is strange that Professor Platt should criticise a film which he has never seen, and of which he has read only a brief account Nevertheless, I look forward to spending a pleasant half-hour with him, showing him the film, and providing some relevant references

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Compare, for instance, the quality of the pain of lumbago with the quality of the pain when a patient displaces a cartilage in the knee After the first twenty-four hours a "locked" knee ceases to cause spontaneous pain and is painful only if the patient fails to rest the limb By contrast a severe attack of lumbago will cause spontaneous agony for two or three weeks and resist bed rest and even injections of morphine This persistent spontaneous pain is unlike the response of the body to a simple mechanical displacement, because skeletal tissues rapidly adapt to a displaced fragment and pain will disappear though it will return if function is demanded of the part. It seems to me that the persistent agony of a severe attack of lumbago is more like the pain caused by raised tension inside cavities which resist distension An alveolar abscess or a boil in the external auditory meatus causes pain which persists in a way which could not be imitated by inserting a solid object of the same shape and size as the bead of pus, because the tissues which were stretched by the solid object would adapt themselves and only a fluid mechanism capable of continued expansion could maintain the tension and so maintain the pain One of the most painful complications in orthopædic surgery is a postoperative hæmarthrosis after meniscectomy, if bleeding from a small artery fills the closed cavity of the knee-joint with blood under tension the postoperative pain is so severe that no amount of morphine will render the patient completely comfortable nor will any position of the limb afford relief, and this condition will persist until the tension is relieved

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University Department of Orthopædic
Surgery, Royal Infirmary,
Manchester, 13

JOHN CHARNLEY

BILIARY VESICULAR STASIS

SIR,—I am delighted to see, in Mr Dudfield Rose's article last week, a more critical attitude towards biliary surgery, as with modern methods of investigation the time has long passed when blind cholecystectomy should be performed for obvious or presumed diseases of the biliary tract

I have no personal experience of manometry, which is especially popular with French surgeons However, serial cholecystograms and especially operative cholangiography are imperative in order to reveal conditions which might otherwise be overlooked Operative cholangiography is a simple and often illuminating procedure, which I have used in over 1000 cases, and I regard it as an essential investigation in an elective cholecystectomy [1]

Mr Rose emphasises that reflex spasm of the sphincter of Oddi is a clinical entity, but he does not mention that a pathological appendix can cause reflex hypertonic vesicular stasis, and in early cases—i e , before the muscle becomes fibrotic—biliary symptoms disappear after appendicectomy

Owing to the disappointing results of blind cholecystectomy no investigation should be omitted which may help in unravelling the complex conditions which affect the biliary tract, and " repeat " operations are not only disappointing to the patient, but are likely to tax the skill and patience of any surgeon

London, W 1

McNEILL LOVE

THE OUTPATIENT DEPARTMENT

SIR,—I was glad to see your annotation of May 10, and I agree with Dr Emslie and Dr Fry

To Dr Fry's three main roles of the outpatient department—consultation, diagnostic, special investigation and treatment centre—I would add a fourth that of teaching centre for undergraduates and postgraduates, as illustrated in a contribution to the Widdicombe File [2] some years ago

As you remark, much capital needs to be devoted to improving the outpatient department, but there is another no less urgent investment, and that is *in men* The outpatient department requires no less adequate staffing than the ward Greater good would be done to more patients if the best physicians spent more time in outpatients, where there is the greater challenge, and less time at the bedside

Seven years ago the Hadassah Medical Organisation inaugurated Medical Outpatient Department C, staffed by full-time physicians In this unit, 18,000 patients have been treated There are 2000 visits a month, including 200 by new patients 12 patients a month are referred for medical admission and 5 more patients to the surgical wards Many patients are saved the need of hospital beds, and patients who cannot be admitted, or who refuse admission, are often able to get essential treatment in outpatients Undergraduates and postgraduates find there a representative cross-section of the world of practice There are also special problems, such as how to treat patients living in bad environments, and how best to supplement the training of younger doctors in the outpatient department

Outpatient work of a high standard requires (1) physicians whose first interest is in the patient, (2) time to listen and to examine and to answer the patient (which means adequate staffing), (3) consultative services in the specialties, (4) laboratory and radiological services, (5) good records and records office, (6) recovery-observation beds, (7) research work based on the outpatient

The success and prestige of an outpatient department depend on the active presence of senior staff and their encouragement by the administration and, in a teaching hospital, by the Faculty

A good outpatient department is an expensive undertaking, but without it health services cannot be run economically, efficiently, or humanely

Mayer de Rothschild
Hadassah University Hospital,
Jerusalem

ELI DAVIS
Chief, Medical Outpatient Clinic C

TIME AND THE NERVOUS SYSTEM

SIR,—I fully sympathise with Professor Russ's difficulty (expressed in his letter last week) in grasping " Professor Woodger's definition of Time " because there is no such thing, and the non-existent is notoriously difficult to grasp Let us hope that there will always be no such thing What was offered was a definition of " clock "—which is quite a different matter Confusing " time " with " clock " is like confusing " space " with " foot-rule "

I was glad to see Professor Russ's reference to Robb, because Robb's work has been sadly neglected—perhaps because it appeared (if memory fails me not) at the beginning of the first world war But it does not do Robb justice to say that " he proposed that Time is simply a matter of ' before ' and ' after ' " What he did was to construct axiomatically a theory of spatiotemporal relations which he called the theory of Conical Order In this he introduced the notion of *after in time* as an undefined notion In my first attempt to use the axiomatic method in biology (1937) I used *before in time* as an undefined notion If you have either of these the other can be defined as its converse Surely before and after are not attributes as Professor Russ calls them but relations, and in that case what can it mean to speak of " the span between them " ? It is only the terms which stand in these relations to one another that can have (some of them) a span between them, and that span is itself a term in the relation

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J H WOODGER

THE PLACE OF HUMAN BIOLOGY IN *MEDICAL EDUCATION*

SIR,—I am bound to agree with Dr Scott (June 21) that Dr Tanner's suggested preclinical curriculum (June 7) seems rather long and rather diffuse And I agree with Dr Scott again that much of our present trouble can be traced to the unreal and misleading separation of anatomy, physiology, and pathology As he says, the important thing is that anatomy and physiology should be understood, not merely memorised They cannot really be understood in isolation from one another, nor can pathology be understood in isolation from physiology and anatomy

A similar attitude should in my opinion be adopted towards physics, chemistry, and biology I do not think that the student will " for all practical purposes have done enough at school " He may have done enough to gain exemption from 1st M B , but he will not have done enough to understand these subjects and their bearing on his later studies Just as Dr Scott recommends that anatomy and pathology should run through the whole curriculum and on into postgraduate work, so should our knowledge and understanding of the basic sciences be enlarged by constant references to them throughout our working lives Thus we may better understand what we are trying

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1 Love, McN *Brit J Surg* 1952, 40, 161
2 *Lancet*, 1954, ii, 420

to do in the course of our medical practice. Thus we can move more and more towards scientific medicine and away from empiricism. (There should be no more need than there is at present to introduce a course of instruction on the humanist aspect of our work.)

Perhaps I should add that I write in all humility as one who daily regrets his lack of grasp of the subjects he "learnt" for 1st and 2nd M.B.

How right Dr Scott is about teaching! The art of great teaching must certainly be restored to its proper place. But there are not many great teachers, and they stand out under all circumstances. It is also important that those who like teaching should be encouraged to do it, and that teaching should not be regarded as a chore but as one of the highest of human activities.

Department of Morbid Anatomy,
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R. R. WILSON

COLOURED TABLETS

SIR,—Mr Grainger (June 21) must be aware that green tablets, which are seventh on his list of degree of attraction to children, have been far and away the most frequent cause of accident—I refer to the green tablets of ferrous sulphate.

Surely Mr Grainger is being less than fair to the British Pharmacopœia Commission in his second paragraph. The statement in the introduction to the *B.P. 1958* on the use of colour in tablets is as follows:

> "Permission has been given in a limited number of monographs on tablets for the addition of a suitable colouring agent to the coating because unfortunately uncoloured tablets have not been made available."

This permission in any case applies only to a few coated tablets and not to the majority of tablets contained in the *B.P.*

Ciba Laboratories Ltd.,
Horsham, Sussex.

A. CHAMINGS

PREMEDICATION FOR OUTPATIENT ELECTROCONVULSION THERAPY

SIR,—Dr Collard's letter of June 21 is of interest at this time when we are concerned in making electroplexy as safe a procedure as possible.

In my limited experience of both general-hospital and mental-hospital practice, I have found that resistance among patients to pretreatment usually responds to simple explanation and sympathetic reassurance.

Before recommending premedication in addition to thiopentone and relaxants it might be worth while bearing in mind certain points which Dr Collard does not mention.

(*a*) That cumulative and/or synergistic effects of premedication plus thiopentone and relaxants might be expected to cause an increase of respiratory depression and postconvulsive apnœa.

(*b*) That there might perhaps be an increased number of subshocks received by the patients, which in themselves, although not harmful, might necessitate either stepping up the voltage or a greater number of attendances for the patient in order to produce satisfactory remission, and in the event of increasing the voltage, the possibility of neuronal damage being produced in some patients—e.g., recurrent endogenous depressives—who may require several courses of treatment.

(*c*) Whether premedication diminishes postconvulsive confusion, which in my experience is complained of more by patients than pretreatment anxiety.

In view of the fact that the use of thiopentone and relaxant drugs for electroplexy has been associated with an increase of mortality, it is desirable to adopt a critical attitude towards the addition of what may be a further risk to the patient, unless the results of properly controlled experiments show otherwise.

St James's Hospital,
Leeds

MARSHALL FRIEZE

NEW LIGHT ON MOLLUSCUM SEBACEUM

SIR,—May I be allowed to comment on your interesting leading article of June 7? The red margin of the lip is a site on which these tumours may arise, though the idea that they can occur here had been resisted by those who believed in the pilosebaceous origin. Since I published my first case,[1] "kerato-acanthoma of the lower-lip red margin", I have collected others. Spontaneous regression was noted and shown in the published photographs, and was complete. To fit in with the theory of origin the red margin of the lip should contain pilosebaceous follicles. According to the anatomists the lips, though hairless, may contain sebaceous glands. Do these show cyclical activity?

Cambridge.

C. HOWARD WHITTLE

ANÆSTHESIA FOR THE EMPHYSEMATOUS

SIR,—In your annotation of June 14 you discuss the special difficulties of anæsthesia in the presence of respiratory insufficiency and state:

> "Unfortunately there is as yet no simple way of estimating the gas tensions of arterial blood, but, if metabolic alkalosis can be excluded, the serum-bicarbonate content of venous blood will indicate whether or not carbon-dioxide retention is present."

In our experience this simple test may be seriously misleading if given the interpretation you suggest. In the accompanying table we give the blood-gas findings in four patients suffering from moderate to very severe CO_2 retention following anæsthesia and surgery.

Case	Time	Plasma				Blood
		T CO_2 (mM per l)	H_2CO_3 (mM per l)	pH	pCO_2 (mm Hg)	O_2 satn. (%)
1	Immediately postop	30·8	28·3	7·15	83	93
2	Immediately preop	37·0	34·8	7·29	75	70
	Postop	34·9	30·5	6·94	147	85
3	Postop	24·1	20·0	6·79	137	42
4	3 hr postop	30·4	26·4	6·92	133	90

Of these patients, cases 1, 3, and 4 almost certainly had normal electrolytes and blood-gas tensions before operation. Despite severe CO_2 retention their plasma-T CO_2 and bicarbonate levels remained within the normal range. Case 2 had emphysema and elevated T CO_2 before operation. Postoperatively the T CO_2 had fallen slightly. This was not associated with improvement in the CO_2 retention but with serious aggravation of it.

The reason why the plasma-T CO_2 fails to rise to the levels expected in severe CO_2 retention is that anæsthesia itself, especially if there is anoxæmia, is associated with metabolic acidosis which depresses the level of plasma bicarbonate. The resulting level of plasma-T CO_2 is therefore a balance between two influences working in opposite directions.

This problem cannot be resolved by making one measurement on blood. Two measurements are necessary: the blood-pH and the plasma-T CO_2. The former estimation can be done in a few minutes with modern techniques, and therefore we suggest that your final sentence should have read: "Few will dispute that facilities for determining the blood-pH and plasma-T CO_2 level should nowadays be available to the anæsthetist."

Surgical Unit,
St. Mary's Hospital,
London, W 2.

VICTOR WYNN
DAVID BROOKS

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[1] *Lancet*, 1957, i, 1019.

HOOKWORM AND ANAEMIA

SIR,—Dr Meiklejohn and Dr Passmore (April 19) suggest that diet is the main factor in the anæmia associated for so long with hookworm infestation in the tropics I would agree with Sir Philip Manson-Bahr (May 3) that diet has little if anything to do with the anæmia

Among tea-garden labour in Assam we see a good deal of anæmia even though the malarial type is now almost extinct When patients who are investigated and found to have hookworm infestation alone are treated for this the improvement is dramatic with no alteration in diet, and they are indeed treated as outpatients so that there can be no change

As regards the financing of further research, I would point out that the Indian Tea Association financed a long and extensive survey carried out by Dr Foy and Dr Kondi in 1955 on the causes of anæmia in Assam, and their conclusions coincided with the less expert opinion of the tea-garden doctors that is, that hookworm was one of the causes, be it only one, of the many that are found in this area

Panitola P O , Assam D A H McNaught

EFFECT OF PREDNISOLONE ON VITAMIN-B_{12} ABSORPTION IN PERNICIOUS ANÆMIA

SIR,—While studying lactic dehydrogenase (LD) activity in various forms of megaloblastic anæmia, I came across the interesting paper by Doig et al [1] on the response of megaloblastic anæmias to prednisolone I have now observed that vitamin B_{12} not only causes hæmatological remission but also restores to normal the increased LD values found in pernicious anæmia Later, I found that the LD activity also responded to prednisolone

Four cases were studied two patients with pernicious anæmia in relapse, one with pernicious anæmia in remission, and one non-anæmic patient who had had a total gastrectomy for peptic ulcer The results were as follows (the oral dose of B_{12} given in the Schilling test was 1 µg B_{12}-^{60}Co, and an excretion of 2 5% has been regarded as the upper limit in pernicious anæmia)

	Schilling test	
Condition	*After prednisolone*	*Prednisolone discontinued, B_{12} given parenterally*
Pernicious anæmia in relapse	8 8%	1 7%
Pernicious anæmia in relapse	8 6%	3 9%, later 3 1%
	Before prednisolone	*After prednisolone*
Pernicious anæmia in remission	0 1%	2 8%
Total gastrectomy	0 3%	0 4%

Thus, in two patients with pernicious anæmia, who showed improvement of the blood-picture and restoration of the bone-marrow to normal after prednisolone therapy (30 mg daily for 21 days), the Schilling test values also became almost normal When the effect of the prednisolone had subsided and adequate antianæmic therapy had been instituted, the Schilling values fell below normal In the first case a fæcal excretion test (oral dose 1 µg B_{12}-^{60}Co) showed practically normal values (62 8%) after prednisolone

In the third case (pernicious anæmia in remission), where the response to the Schilling test was much decreased before prednisolone therapy (30 mg daily for 7 days), a significantly increased value was obtained after prednisolone By contrast, the patient who had had a total gastrectomy did not respond to prednisolone, as revealed by the Schilling test

These preliminary results suggest that the remission that follows the giving of prednisolone is due to increased absorption of vitamin B_{12}, which in turn may be attributable to an increase in the production of intrinsic factor caused by the prednisolone It should be emphasised that the absence of a response in the gastrectomised patient points in the same direction, since in this case cells capable of producing intrinsic factor were lacking

In both cases of manifest pernicious anæmia responding to prednisolone, there was a definite rise in the microbiological serum-B_{12} level during prednisolone therapy (63 to 125 µµg per ml and 46 to 134 µµg per ml, respectively) This also supports the assumption that the remission may have been due to absorption of small amounts of vitamin B_{12} from the intestine

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[1] Doig, A., Girdwood, R H, Duthie, J J R., Knox J D E. *Lancet*, 1957, ii, 966

"A BARE BODKIN"

SIR,—Francis Bacon said that "death will not be denied", William Hunter commented, "How easy and pleasant a thing it is to die", and Hamlet's famous soliloquy refers to the simplicity with which life can be ended I believe that some articles, such as those of Bedford,[1 2] give, perhaps, an unnecessarily gloomy view of the capacity of the human body, however aged, to withstand "the thousand natural shocks That flesh is heir to" The following case is reported in support of this thesis, and because complete recovery from a number of severe cardiovascular accidents at the age of 92 is worthy of record

The patient was a farmer who, at the ripe age of 92, was admitted to hospital under the care of my colleague, Dr J Charles Shee, on May 19, 1957, following a severe hæmatemesis, for which he received transfusions amounting to 8 pints of blood in the first instance He had been most unwilling to enter hospital for treatment, as he had never been ill before, and felt that he would recover more quickly at home on his farm in the bush Surgical opinion was not sought at this time, since his doctor did not think that surgery was likely to be helpful in so old a patient

Medical treatment seemed to have been entirely successful, but the patient suffered a further hæmatemesis on May 21 which necessitated transfusion of 3 pints of blood I first met the patient on May 24, when he had had another severe hæmatemesis I reached the bedside in response to an urgent summons, to find a cheerful old gentleman, "a man not old, but mellow, like good wine", whiter than the sheet, with obvious evidence of a massive hæmatemesis, receiving blood through veins in both arms, and glucose solution through his right long saphenous vein Even this did not seem to be adequate to replace the amounts he had lost and was losing His cardiovascular age seemed, however, to be less than his chronological age, for in spite of his shocked condition he was sufficiently alert to lay down a most exact therapeutic regimen in the whispered words, "Cut me quick, Doc, or I'm a goner"

This succinct assessment of the situation was so patently correct that the operation began less than thirty minutes later Laparotomy disclosed a large gastric ulcer astride the left gastric artery about 2 in below the œsophagogastric junction Fortunately, although a chronic ulcer, it had not penetrated any other viscus, and a rapid partial gastrectomy was comparatively easy to perform The left gastric artery was controlled as early as possible, and his condition improved considerably as soon as this step had been completed

His condition at the end of the operation was fairly good, and he made good progress until the second postoperative day, when he seemed very shocked This was due to the onset of auricular fibrillation, which was controlled within forty-eight hours by digoxin He then made an uninterrupted recovery until seven days later, when he complained of severe upper abdominal pain, and once again looked *shocked and ill* This setback was due to a moderate-sized anterior myocardial infarct, which responded to treatment

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[1] Bedford, P D *Lancet*, 1956, ii 750
[2] Bedford, P D *ibid* 1957, ii, 505

From this time onwards, his condition never gave rise to any anxiety, and he left hospital on June 20, in excellent general condition, and with his fibrillation controlled

Recently, he sent me a present of some biltong, prepared from a buck which he had shot to celebrate his 93rd birthday, surely adequate confirmation of the completeness of his recovery

The main interest of this case is its demonstration of the recuperative powers of such an aged patient, following two severe and one torrential hæmatemeses, auricular fibrillation, and a myocardial infarct, all within the space of some fourteen days In spite of all these serious insults to his cardiovascular system, and the stress of a major surgical procedure, he made a complete recovery, thereby demonstrating, once again, that " a man is as old as his arteries "

I should like to express my thanks to Dr J Charles Shee for his help in the management of this patient, both before and after operation, for without his skill the patient would not have survived At least an equal tribute must be paid to Dr Ian Michie, who administered the anæsthetic

Bulawayo, Southern Rhodesia. WILLIAM HOUSTON

DEATH OF A BOXER

SIR,—In reference to Dr Compton Smith's letter last week, I cannot recall any cases of cerebral injury or indeed meeting any punch-drunk boxers in my long association with both amateur and professional boxing Injuries can of course take place if a man cannot defend himself, but the trained referees of the A B A and B B B C in consultation with their medical advisers are always vigilant to prevent men entering the ring in an unfit condition of health They are also quick to stop a contest if a man is badly outmatched and suffering any serious injury before or during the fight

Tunbridge Wells E F ST J LYBURN

AUTO-ANTIBODIES IN THYROID CARCINOMA

SIR,—It is now well established [1] [2] that antibodies which precipitate with thyroid extracts can be demonstrated in the serum of patients with lymphadenoid goitre

In testing sera of patients with various thyroid disorders, we found that three out of six cases of thyroid carcinoma had high titres of antithyroglobulin when examined by the tanned-cell hæmagglutination test In two of them, the level of antibody was sufficiently high (titre of 20,000) to give a positive precipitin test by the Oudin method

In the first of these two cases biopsy showed anaplastic carcinoma and areas histologically resembling lymphadenoid goitre In the second case, treated by hemithyroidectomy, examination of many blocks of the excised lobe showed replacement of all normal thyroid tissue by papillary carcinoma (no tissue was available from the remaining lobe, which appeared slightly enlarged but otherwise normal) The third case had a titre of 640 in the tanned-cell hæmagglutination test and the Oudin test was negative Examination of the thyroid gland revealed both anaplastic carcinoma and lymphadenoid goitre

The clinical distinction between thyroid carcinoma and lymphadenoid goitre may be difficult, and until recently the ultimate diagnosis often depended on microscopic examination of the gland Abnormal flocculation reactions or positive precipitin tests may now be taken to favour a diagnosis of lymphadenoid goitre, but, judging by our experience, the finding of positive serological (precipitin) tests does not justify a firm diagnosis of lymphadenoid goitre unless there is other strongly suggestive clinical or biochemical evidence Lymphadenoidal goitre may well predispose to the subsequent development of carcinoma, and the two conditions may be present together Although surgery is now seldom indicated as a definitive form of treatment for lymphadenoid goitre, surgical assistance should be freely invoked to establish a certain diagnosis

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A E STUART
W S A ALLAN

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[1] Roitt, I M , Doniach, D , Campbell, P N Vaughan Hudson, R. *Lancet*, 1956, ii, 820

[2] Roitt, I M , Campbell, P N , Doniach, D *Biochem J* 1958, 69, 248

THE TOURNIQUET

SIR,—I congratulate you on your leading article of May 31

I hold it very necessary to popularise, among surgeons, the aversion towards that horrible medieval instrument that is the tourniquet In this sense, I go much further than Professor Pannett, since I use neither the tourniquet nor any other kind of temporary hæmostasis for any limb operation—not even for amputations [1] I believe that the immediate and late complications of amputation have thereby been avoided—especially stump neuralgias and phantom limbs Progress after operations on bone, nerve or tendon has been excellent The systematic hæmostasis introduced, step by step, during the operation, maintains a normal blood-supply and avoids the serious disturbance caused by ischæmia and reactional hyperæmia

Barcelona M BASTOS ANSART

TETANUS

SIR,—In a leader in your issue of May 10 it was suggested that Hippocrates gave the first description of tetanus and of its usually fatal outcome However, the remarkable author of the Edwin Smith papyrus (19th century B C) (which is thought to be a copy of an earlier work, possibly dating back to the building of the Pyramids —i e , to the 30th century B C [2]) describes the following clinical picture

Examination If thou examinest a man having a gaping wound in his head, penetrating to the bone (and), perforating the sutures of his skull, thou shouldst palpate his wound, (although) he shudders exceedingly Thou shouldst cause him to lift his face, if it is painful for him to open his mouth, (and) his heart beats feebly, if thou observe his spittle hanging at his two lips and not falling off, while he discharges blood from both his nostrils (and) from both his ears, he suffers with stiffness in his neck, (and) is unable to look at his two shoulders and his breast

First diagnosis Thou shouldst say regarding him "One having a gaping wound in his head, penetrating to the bone (and) perforating the sutures of his skull, the cord of his mandible is contracted, he discharges blood from both his nostrils (and) from both his ears, while he suffers with stiffness in his neck An ailment with which I will contend "

Second examination If then, thou findest that the flesh of that man has developed fever from wound which is in the sutures of his skull, while that man has developed ty' (untranslatable) from that wound, thou shouldst lay thy hand upon him Shouldst thou find his countenance is clammy with sweat, the ligaments of his neck are tense, his face is ruddy, his teeth and his back (?) the odor of the chest of his head is like the BKN (urine) of sheep, his mouth is bound, (and) both his eyebrows are drawn, while his face is as if he wept

Second diagnosis Thou shouldst say regarding him " One having a gaping wound in his head, penetrating to the bone, perforating the sutures of his skull, he has developed ty', his mouth is bound, (and) he suffers with stiffness in his neck An ailment not to be treated " ?

Third examination If, however, thou findest that that man has become pale and has already shown exhaustion

Third treatment Thou shouldst have made for him a wooden brace (or tube) with linen and put into his mouth

*Gloss B** As for "The cord of his mandible is contracted", it means a stiffening on the part of the ligaments at the end of his ramus, which are fastened to his temporal bone, that is at the end of his jaw, without moving to and fro, so that it is not easy for him to open his mouth because of his pain

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[1] Bastos Ansart, M Tratado de Operatoria Ortopedica y Traumatologica. Barcelona, 1957

[2] Husein, K. *J Bone Jt Surg* 1949, 31B, 309

* These are glossaries given in the original papyrus as explanatory notes to the text. They were probably written by later copyists

Gloss E As for "The ligaments of his neck are tense" it means that the ligaments of his neck are stretched stiff by reason of his injury

Gloss I As for "His mouth is bound, (and) both his eyebrows are drawn, while his face is as if he wept", it means that he does not open his mouth that he may speak, both his eyebrows are distorted, one drawing upward, the other drooping downward, like one who winks while his face weeps

This gives a very objective description of trismus, neck rigidity, and risus sardonicus (?), following a wound of the head, and ending fatally The phrase "an ailment not to be treated" meant in old Egyptian texts a fatal outcome, in contradistinction to "an ailment I shall treat" and "an ailment with which I will contend" which were used to signify a good and a doubtful prognosis respectively

The possibility that this description meant meningitis cannot, of course, be excluded The necessity of placing a wooden brace (or tube) between the teeth and the other signs make it very likely, however, that it meant tetanus

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PAUL GHALIOUNGUI

THE RUSSIAN VACCINE

SIR,—It is surely absurd that this substance should be used for the treatment of disseminated sclerosis, when it is quite untested for this purpose and, as far as I can make out, is not even being used in Russia for treatment of this disease I am frequently asked about its use and have no hesitation in saying that as far as I can judge it is useless for cases of disseminated sclerosis, and should not be used as it might be harmful

Oxford

W RITCHIE RUSSELL

DIETARY RESTRICTION AND COAGULABILITY OF BLOOD

SIR,—I read with great interest the article by Dr McDonald and Miss Edgill in your issue of May 10 We reported in our letter of Feb 8 the results of our investigations on hypercoagulability and "heparin loading test" As we had pointed out,[1–3] our "heparin loading test" can reveal hypercoagulability

In patients with hypercoagulability, the level of cholesterol, total lipid, and phospholipid were increased and at the same time there was an increase of β-lipids and a decrease of α-lipids in lipidograms

In cases showing hypercoagulability according to the heparin loading test, three to six months of strict low-fat diet with or without anticoagulant treatment, hypercoagulability decreased or became normal (50 mg heparin twice weekly intravenously) Further details will be published later

The remark of Dr McDonald and Miss Edgill about the parallel between the cholesterol level and platelet-stickiness is of considerable importance

We, too, have observed[3 4] the connection between the blood-lipid level and platelet function

In the course of our studies[3–5] of the hæmorrhagic diathesis in liver diseases, we drew attention to the fact that when cholesterol and cholesterol esters were much diminished, α-lipids almost disappeared and β-lipids decreased, whereas the agglutinability and adhesiveness of the platelets were much reduced or lost and the bleeding-time was prolonged

At the same time, there was a large reduction in the formation of thromboplastin (Biggs and Douglas's test) due to a defect in platelet suspension The platelets did not contain the thromboplastic factor (phospholipid) in other words, a secondary thrombopathia was observed[3] in liver disorders

As Dr McDonald and Miss Edgill have shown, and our observations have confirmed, there is a close relationship between the level of blood-lipids and platelet functions

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ORHAN NURI ULUTIN

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[1] Ulutin, O N, Sestakof D *Lancet*, 1958 i, 324

[2] Ulutin O N, Sestakof D *Bull Soc turq Méd* 1957, 23, 689

[3] Ulutin O N Study of the Formation of Thromboplastin in Hæmorrhagic Disorders Istanbul 1957

[4] Berker, F, Ulutin, O N, Karaca, M, Sestakof D *Bull Soc turq Méd* (in the press)

[5] Ulutin, O N, Karaca M *ibid* 1956 22 473

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—I studied with great interest Dr Mason and Dr Black's case-report in your issue of April 26 I especially admired the thoroughness and objectivity of the presentation

Apparently without realising it, they submitted this patient to one form of conventional "desensitisation" therapy—namely, the parenteral administration (either subcutaneously or intradermally), co-seasonally, of very minute amounts of pollen extracts This method of treatment is extremely effective in all patients with pure pollen allergy, and is especially effective when preceded by a course of relatively high-dosage therapy, which, I presume, is what the patient actually had (during the previous season)

A very interesting clinical feature is the "cold in the head", contracted during the "second week of June" This episode was undoubtedly allergic in nature, especially in view of the specific response to ephedrine It probably occurred between the clinic visits of week 7 and week 8, if we assume that week 1 was represented by April 29 *What is interesting is the fact* that during the two visits immediately preceding (weeks 6 and 7), she was given intradermal injections only in the left arm, whereas on all of the other visits, if we consider only the span of the height of the pollen season, she was given injections in the left leg as well as the left arm In other words, for weeks 6 and 7 she received only *half* the usual dosage It is entirely possible that this half dosage was slightly less than this patient's particular requirement for this particular pollen season If so, the accumulated deficiency of two weeks' underdosage could well explain the allergic symptoms described as a "cold in the head"

Nevertheless Dr Mason and Dr Black have made an important contribution—namely, their demonstration of the relationship between psychomotor factors and skin reactivity And this, after all, is the main theme of the article, judging by its title

We have continually noted that, in any given group of patients, there is a remarkable lack of correlation between the relative severity of clinical symptoms and the relative intensity of skin reactions For example, one patient may have very weak (although perhaps highly specific) skin reactions, but very severe *clinical symptoms* Another patient may have very strong skin reactions with very mild clinical symptoms

This same lack of correlation is observed whether or not the patient has had any "desensitisation" therapy Some patients who have been clinically cured by "desensitisation" therapy will nevertheless *retain their skin reactivity*, at least to some definite degree On the other hand, some patients will have relatively rapid diminution of skin reactivity early in the course of treatment, even though their clinical symptoms may not yet be under control

This quantitative dissociation between skin reactivity and clinical symptoms has been a source of many misunderstandings and much confusion Many explanations have been offered by various investigators, but they usually add to the confusion

The observations of Dr Mason and Dr Black lend some objective evidence, which, if properly interpreted and followed up, may help to lead us out of our bewildered state Their observations suggest that, even though skin reactivity is specifically related, *qualitatively*, to clinical allergic manifestations, the actual *intensity* of the skin reactions may be strongly influenced by purely psychomotor factors

On the other hand, they have not proved anything conclusive about the relationship between psychomotor factors and clinical allergic manifestations In fact, on the basis of the data given, we cannot conclude that psychological treatment played any important role whatsoever in relieving the allergic symptoms of the patient.

There is no question but that hypnosis, and other forms of psychiatric treatment, occupy an important and very respectable place in the treatment of allergic disease, but I seriously doubt if the psychiatric approach will ever justifiably assume the dominant role

The only notable exception might be in the neurotic adult patient, who has recovered from a severe childhood allergy, but whose strong "psychiatric residual" causes him, under certain circumstances, to re-enact certain "allergic" symptoms In such a case, the psychiatric factor is unquestionably dominant, and hypnosis could very well be the most effective treatment. However, contrary to general opinion, such cases are surprisingly uncommon.

For the vast majority of patients with atopic allergy there is not, as yet, any substitute for the following principles of treatment

(1) *Avoidance of the offending antigen or antigens* —This is imperative in all cases of food allergy, and all cases of "environmental" allergy (house dust, feathers, animal danders, &c)

(2) *Control of infection* —Acute or chronic bacterial infections, involving any organ or system of the body, will usually aggravate atopic allergy manifestations, even though the latter may be expressed in an entirely different organ or system Prompt treatment with antibiotics is generally indicated

(3) *"Desensitisation" treatment* —This is often a very important aspect of the treatment of "environmental" allergy, although not necessarily so in small children and infants It is the only effective treatment for pollen allergy, regardless of the patient's age

CHARLES R COWAN
Chief of Allergy Service.

U S Army Hospital, Paris

METHOD FOR THE ASSAY OF PROPERDIN

SIR,—The work of Pillemer et al[1] with properdin showed the important role of aspecific factors in natural resistance to infection and illustrated the interesting interactions of this principle with the components of the C′ It can now be said that both these points have been confirmed[2-6] Some difficulties are met, however, in carrying out the assay of properdin, as proposed by the discoverers of this factor It has therefore been suggested that properdin activity be measured by other methods based on different principles (hæmolysis of tanned cells, bacteriolytic activity, &c) Our experience has not, however, been entirely satisfactory with these procedures

In recent months we have tested a new method for the estimation of properdin with better results The principle is that described by Pillemer et al[1] which uses a polysaccharide prepared from yeast cells—zymosan

Our technique entails careful absorption of the sample of properdin by double incubation at 17° C with a standardised amount of inulin, an insoluble polysaccharide which has some advantages over zymosan[3] Serial dilutions of the properdin-inulin complex are then incubated for one hour at 37° C with a fixed amount of RP (properdin-free serum) formed from the supernatant of the tube previously incubated at 17° C, and 1 ml of sensitised cells is added

The optical density of hæmolysis, read photometrically, is inversely proportional to the properdin value The C′3 titre of the sample under examination is each time determined by R3 (C′3-free serum) Controls are necessary to ascertain total absorption of properdin and the reliability of the other reagents

With this procedure it is possible to overcome some difficulties of Pillemer's method for the preparation of suitable RP As is known, only a few sera (5–10%) prove useful for the preparation of RP The RP prepared from the sample under examination is a good reagent for the properdin determination of the same serum On the other hand, in the procedure here outlined the C′3 activity of the system is precisely determined, while in Pillemer's method no reference is made to the C′3 titre of the sample test

We have performed more than 60 properdin determinations with constant and reproducible results In normal subjects properdin varies within narrow limits The value is lower in older than in young people Research on sera in pathological conditions is now in progress

Institute of Medical Pathology,
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V BIANCHI
G GHIRARDO

GLUCURONIDE SYNTHESIS IN FŒTAL LIVER AND KIDNEY

SIR,—Glucuronides are synthesised in adult liver by enzymic transfer of glucuronic acid from uridine diphosphate glucuronic acid (U D P G A) to an acceptor substance,[1,2] which can be bilirubin[3] It is known that certain newborn jaundiced infants are unable to transfer glucuronic acid to bilirubin in this manner[4]

Recent work,[5] using *o*-aminophenol and (−)-menthol as acceptor substances, has shown a similar defective transference to be characteristic of fœtal liver and kidney in the guineapig, mouse, and probably other species In the liver, and possibly in the kidney, the phenomenon is explained by deficiency of both the enzyme (U D P -transglucuronylase) and U D P G.A Levels of both increase up to birth, and it seems that the amount of liver U D.P G A available is to some extent a limiting factor That the same microsomal enzyme is being studied as the one transferring glucuronic acid to bilirubin is probable from the reduced synthesis of both phenyl and bilirubin glucuronides in congenitally jaundiced adult humans and rats[6]

By the kind cooperation of Prof J Walker and the staff of the department of midwifery, Queen's College, two normal human fœtuses of 3–4 months were studied by this method In both, negligible amounts of liver enzyme and U D P G A , or of kidney glucuronide formation, were found Results were also negative for placenta

It may be that certain types of neonatal jaundice are due to persistence of this fœtal metabolism, particularly in premature infants Administration of U.D P G A might therefore prove of use, where its lack is the limiting factor, but there seems no explanation of the claimed relief of this condition by oral treatment with glucuronate,[7] an ion which does not increase the enzyme action in vitro[1] Attempts to induce glucuronide formation by administration of glucuronidogenic drugs could lead, in cases of low U D P -transglucuronylase, to competition with bilirubin at the already deficient enzyme molecules

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Queen's College, Dundee.

G J DUTTON

Obituary

SIR ARNOLD STOTT

J G W writes

Generations of Westminster men will remember with gratitude and affection the clinical teaching of the late Sir Arnold Stott, particularly, perhaps, for two of its outstanding qualities One was the thoroughness of the clinical examination from head to toe, the other was the superb bedside manner—the humblest and poorest of outpatients would receive a "Madam" the graciousness of which would have gladdened the heart of a duchess

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1 Pillemer, L., Blum, L , Lepow, I , Wurz, L., Todd, E *J exp Med* 1956, 103, 1
2. Isliker, H. C., Linder, E *Vox Sanguinis* 1958 3, 23
3 McNall, E G *Proc Soc. exp Biol*, N Y 1957, 84, 399
4 Leon, M A *J exp Med* 1956, 103, 285
5 Barlow, J L , Vunakis, H v , Levine, L. *Fed Proc* 1957, 16 405
6 Soulier J P , Menache, D , Larrieu M *Rev Franc Clin Biol* 1957, 8, 857

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1 Dutton, G J , Storey, I D E. *Biochem J* 1954 57, 275
2. Storey, I D E., Dutton, G J *ibid* 1955, 59, 279
3 Schmid, R., Hammaker, L., Axelrod, J *Arch. Biochem. Biophys* 1957, 70, 285
4 Lathe, G H., Walker M. *Biochem J* 1957, 67, 9P
5 Dutton, G J *ibid* 1958 (in the press)
6 Axelrod J , Schmid, R., Hammaker, L. *Nature, Lond* 1957, 180, 1426.
7 Danoff, S , Grantz, C., Boyer, A., Holt, L. E. *Lancet*, 1958, i, 316

ramus, which are fastened to his temporal bone, that is at the end of his jaw, without moving to and fro, so that it is not easy for him to open his mouth because of his pain

Gloss E As for "The ligaments of his neck are tense" it means that the ligaments of his neck are stretched stiff by reason of his injury

Gloss I As for "His mouth is bound, (and) both his eyebrows are drawn, while his face is as if he wept", it means that he does not open his mouth that he may speak, both his eyebrows are distorted, one drawing upward, the other drooping downward, like one who winks while his face weeps

This gives a very objective description of trismus, neck rigidity, and risus sardonicus (?), following a wound of the head, and ending fatally The phrase "an ailment not to be treated" meant in old Egyptian texts a fatal outcome, in contradistinction to "an ailment I shall treat" and "an ailment with which I will contend" which were used to signify a good and a doubtful prognosis respectively

The possibility that this description meant meningitis cannot, of course, be excluded The necessity of placing a wooden brace (or tube) between the teeth and the other signs make it very likely, however, that it meant tetanus

Faculty of Medicine,
Ein Shams University, Cairo

PAUL GHALIOUNGUI

THE RUSSIAN VACCINE

SIR,—It is surely absurd that this substance should be used for the treatment of disseminated sclerosis, when it is quite untested for this purpose and, as far as I can make out, is not even being used in Russia for treatment of this disease I am frequently asked about its use and have no hesitation in saying that as far as I can judge it is useless for cases of disseminated sclerosis, and should not be used as it might be harmful

Oxford

W RITCHIE RUSSELL

DIETARY RESTRICTION AND COAGULABILITY OF BLOOD

SIR,—I read with great interest the article by Dr McDonald and Miss Edgill in your issue of May 10 We reported in our letter of Feb 8 the results of our investigations on hypercoagulability and "heparin loading test" As we had pointed out,[1–3] our "heparin loading test" can reveal hypercoagulability

In patients with hypercoagulability, the level of cholesterol, total lipid, and phospholipid were increased and at the same time there was an increase of β-lipids and a decrease of α-lipids in lipidograms

In cases showing hypercoagulability according to the heparin loading test, three to six months of strict low-fat diet with or without anticoagulant treatment, hypercoagulability decreased or became normal (50 mg heparin twice weekly intravenously) Further details will be published later

The remark of Dr McDonald and Miss Edgill about the parallel between the cholesterol level and platelet-stickiness is of considerable importance

We, too, have observed [3 4] the connection between the blood-lipid level and platelet function

In the course of our studies [3–5] of the hæmorrhagic diathesis in liver diseases, we drew attention to the fact that when cholesterol and cholesterol esters were much diminished, α-lipids almost disappeared and β-lipids decreased, whereas the agglutinability and adhesiveness of the platelets were much reduced or lost and the bleeding-time was prolonged

At the same time, there was a large reduction in the formation of thromboplastin (Biggs and Douglas's test) due to a defect in platelet suspension The platelets did not contain the thromboplastic factor (phospholipid) in other words, a secondary thrombopathia was observed [4] in liver disorders

As Dr McDonald and Miss Edgill have shown, and our observations have confirmed, there is a close relationship between the level of blood-lipids and platelet functions

Second Internal Clinic of Istanbul
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ORHAN NURI ULUTIN

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[1] Ulutin, O N, Sestakof D *Lancet*, 1958, i, 324
[2] Ulutin, O N, Sestakof D *Bull Soc turq Méd* 1957, 23, 689
[3] Ulutin, O N Study of the Formation of Thromboplastin in Hæmorrhagic Disorders Istanbul 1957
[4] Berker, F, Ulutin, O N, Karaca, M, Sestakof D *Bull Soc turq Méd* (in the press)
[5] Ulutin, O N, Karaca, M *ibid* 1956 22 473

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—I studied with great interest Dr Mason and Dr Black's case-report in your issue of April 26 I especially admired the thoroughness and objectivity of the presentation

Apparently without realising it, they submitted this patient to one form of conventional "desensitisation" therapy—namely, the parenteral administration (either subcutaneously or intradermally), co-seasonally, of very minute amounts of pollen extracts This method of treatment is extremely effective in all patients with pure pollen allergy, and is especially effective when preceded by a course of relatively high-dosage therapy, which, I presume, is what the patient actually had (during the previous season)

A very interesting clinical feature is the "cold in the head", contracted during the "second week of June" This episode was undoubtedly allergic in nature, especially in view of the specific response to ephedrine It probably occurred between the clinic visits of week 7 and week 8, if we assume that week 1 was represented by April 29 What is interesting is the fact that during the two visits immediately preceding (weeks 6 and 7), she was given intradermal injections only in the left arm, whereas on all of the other visits, if we consider only the span of the height of the pollen season, she was given injections in the left leg as well as the left arm In other words, for weeks 6 and 7 she received only *half* the usual dosage It is entirely possible that this half dosage was slightly less than this patient's particular requirement for this particular pollen season If so, the accumulated deficiency of two weeks' underdosage could well explain the allergic symptoms described as a "cold in the head"

Nevertheless Dr Mason and Dr Black have made an important contribution—namely, their demonstration of the relationship between psychomotor factors and skin reactivity And this, after all, is the main theme of the article, judging by its title

We have continually noted that, in any given group of patients, there is a remarkable lack of correlation between the relative severity of clinical symptoms and the relative intensity of skin reactions For example, one patient may have very weak (although perhaps highly specific) skin reactions, but very severe clinical symptoms Another patient may have very strong skin reactions with very mild clinical symptoms

This same lack of correlation is observed whether or not the patient has had any "desensitisation" therapy Some patients who have been clinically cured by "desensitisation" therapy will nevertheless retain their skin reactivity, at least to some definite degree On the other hand, some patients will have relatively rapid diminution of skin reactivity early in the course of treatment, even though their clinical symptoms may not yet be under control

This quantitative dissociation between skin reactivity and clinical symptoms has been a source of many misunderstandings and much confusion Many explanations have been offered by various investigators, but they usually add to the confusion

The observations of Dr Mason and Dr Black lend some objective evidence, which, if properly interpreted and followed up, may help to lead us out of our bewildered state Their observations suggest that, even though skin reactivity is specifically related, *qualitatively*, to clinical allergic manifestations, the actual *intensity* of the skin reactions may be strongly influenced by purely psychomotor factors

On the other hand, they have not proved anything conclusive about the relationship between psychomotor factors and clinical allergic manifestations In fact, on the basis of the data

Notes and News

A NEW POLIOMYELITIS CENTRE

ON June 25 the Earl of Limerick, chairman of the Medical Research Council, opened the laboratory buildings of the poliomyelitis centre which is being set up at the Hendon Isolation Hospital, London. Lord Cottesloe, the chairman of the North West Metropolitan Regional Hospital Board, recalled that in 1951 the Poliomyelitis Committee of the Royal College of Physicians of London, under the chairmanship of Sir Charles Symonds, had suggested that a research unit was needed for the investigation of problems concerned with the established disease, and donations of £12,000 from the National Fund for Poliomyelitis Research and of £8000 from the Sir William Coxen Trust had now enabled the laboratory to be built.

As it was thought essential that research should be carried out during the infectious stage of the disease as well as later, it was decided to build the centre at an infectious diseases hospital in close touch, geographically and administratively, with an orthopædic hospital. On the recommendation of Mr H J Seddon, who was responsible for the planning of the centre, Hendon Isolation Hospital was chosen. Over many years the hospital has worked in close cooperation with the Royal National Orthopædic Hospital at Stanmore, and the secondment of nurses and physiotherapists from Stanmore to Hendon will ensure that patients are looked after by the same staff at the two hospitals. Dr A B Kinnier Wilson, a Medical Research Council worker, already attached to the Royal National Orthopædic Hospital where he was working on respiratory problems in poliomyelitis, is now in charge of the laboratory at Hendon, supported by a number of clinicians. If work on poliomyelitis comes to an end the situation of the centre and its link with the Virus Reference Laboratory at Colindale make it a suitable place for the investigation of other virus disorders affecting the nervous system.

The Institute of Orthopædics of the University of London is responsible for the affairs of the centre, but because of its intimate connection with the Hendon Isolation Hospital a coordinating committee has been appointed on which members of the regional medical service, as well as of the Institute of Orthopædics and Royal National Orthopædic Hospital, will serve.

The building is of ingenious design. It is inexpensive and made of a Malayan hardwood called keruing which is as hard as teak, has excellent insulating properties, and needs neither paint nor other preservative. The laboratory was designed by Mr. Lindsay Drake, A.R.I.B.A., of Fry, Drew, Drake, and Lasdun, with the aid of Mr Michael Smythe, A.R.I.B.A., of the Nuffield Foundation.

A FAMILY GUIDE

THE family of a patient who has had a mental breakdown are often frightened and unhappy. They are faced with an illness which they do not understand and therefore fear. Though they are anxious to help, they are uncertain how best to do so. They may feel cut off from the patient by the change that has come over him, they may feel cut off from their neighbours by an unreasonable feeling of shame. Though the healthy and growing change in the public attitude towards mental illness is steadily easing many of these difficulties, there still remains room for the useful guide for the patient's family which the National Association for Mental Health have published.[1]

In the course of relating the story of Jim Thomas who had a mental breakdown, and Alice his wife who had to cope, the booklet gives a clear and honest description of our mental health services and procedure for admission to hospital. It does not suggest that they are perfect, but it makes clear that they can offer help and the hope of recovery to most patients. If community treatment is to prove as successful as we all hope, the family will play an increasingly important part in the patient's treatment, but home is not necessarily the best place for the patient at every stage of his illness. The guide gives a good description of life in hospital, from the point of view of the patient and his relatives, and explains that the family should not feel guilty for arranging for the patient to go there, their turn will come later in helping him to adjust himself to normal life again after he returns home.

Illness, mental or physical, must throw a burden on any family. This guide will help the families of the mentally ill to shoulder theirs with confidence and courage.

AN OPERATING-THEATRE SPOTLIGHT

Mr P Dawson-Edwards and Dr W N Vellacott write:

One of us (P. D-E.) has twice recently described parallel-beam spotlights which it was considered could be made "at home" by hospitals with engineers willing and able to undertake this type of work.[1] The majority of hospitals, however, are probably not in this position, and a commercial firm was therefore approached with a view to the production of such a spotlight. This lamp is now on the market.

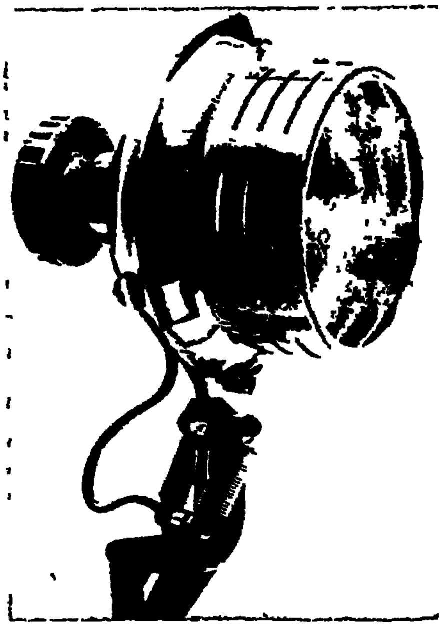

Fig 1—Close-up of lamp showing easily detachable filter holder

It is basically the smaller Lucas "Flamethrower", a lamp noted for its extremely powerful parallel beam. To ensure that the beam is virtually "cold", it is made to pass through a disc of Chance's ON 20 glass, which filters out 90% of the heat and yet transmits 90% of the light. This filter is mounted in a slotted holder which spaces it from the lamp, thus allowing it to be cooled on both sides. The holder is neatly clipped to the lamp housing and can readily be removed for cleaning by releasing the two retaining screws on the front of the lamp (fig 1). An aluminium bulb-shield ensures that there is no dazzle except in the direct line of the beam. The use of a special axial coiled coil bulb provides an even pattern of light of 7 in. diameter which never requires refocusing.

The lamp is mounted on a specially designed 'Anglepoise' arm which makes adjustment both easy and positive through an almost universal range of movement. A plastic handle is fitted to direct the beam. The anglepoise arm can itself be swivelled on the main column. The base of this column, suitably weighted, contains a 12-volt transformer. The finish is in cream with chromium-plated lamp and fittings, and the wheels are of the regulation conducting type (fig 2).

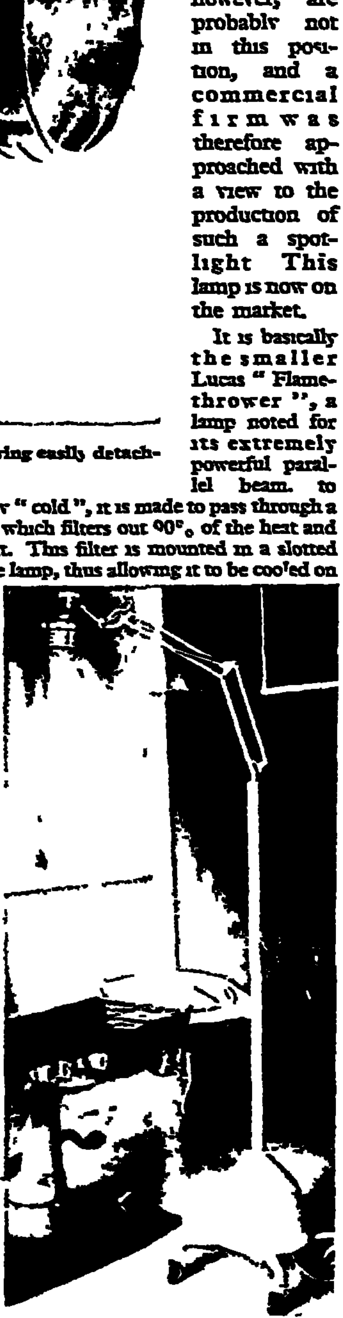

Fig 2—Complete lamp showing base with fully enclosed transformer

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[1] Mental Breakdown. 1958 Pp 28 2s 6d Obtainable from the Association, 39, Queen Anne Street, London, W 1, postage 4d.

[1] *Lancet*, 1955, i, 849, *ibid* 1957, ii, 525

The lamp has been thoroughly tested It has been found particularly helpful in operations deep in the thorax, the abdomen, or the pelvis, it is usually best used in conjunction with normal overhead lighting, and sometimes only for quite short periods during an operation It has also found favour with ophthalmic surgeons, and it has been in constant use in casualty departments The spotlight is always in focus, is very bright, and is astonishingly easy to manœuvre

This spotlight may be obtained from Messrs Herbert Terry and Sons Ltd, Redditch, or their agents

University of London

The board of governors of Queen Charlotte's Hospital and the Chelsea Hospital for Women have set aside £50,000 of their endowment funds for the endowment of a chair of obstetrics and gynæcology at the Institute of Obstetrics and Gynæcology

University of Leeds

At recent examinations the following were successful

M B, Ch B—Margaret Barber, Pauline Bittner, Norman Carr, Frank Carter, Margaret E Coles, A J K Dore, M W Flowers, Gillian M Foster, R D Jackson, J N Lambton, P B Pickles, Stanley Sorkin, Freda M Tomlinson, B K Turnbull, R K Wright

D P M—John Blackburn, Margaret W Galley, Mary Jones, H B Kidd, J T Rose, Brian Ward

University of Liverpool

Dr K McCarthy and Dr K R Dumbell have been appointed senior lecturers in bacteriology, and Dr J L Braithwaite and Dr E W Macmillan senior lecturers in anatomy

University of Manchester

At a recent examination the following were successful

M B, Ch B—J W Aspinall, Roy Battye, F H Brindle, D B Brookes, J E Brooks, A L Buckley, Eric Charles, P J Cox, J S Cumming, Barry Deakin, B H Delany, G G Duckworth, R M Flinn, Joyce Harris, Roy Haworth, Patricia A Hegarty, Raymond Holmes, Alexander Hopkins, W H Isbister, Maria Z Kozubowska, R J Lawton, I P McEwan, A C Peterson, J D Rhodes, P H Roberts, Martin Ryan, Elizabeth M Spencer, Roy Statham, Garo Tahta, Peter Watson, J M Watts, B K Wignall, J D G Williams, S K Wood, P B Wrigglesworth

Queen's University, Belfast

Dr T K Marshall has been appointed to a lectureship in pathology (forensic medicine)

Royal College of Surgeons of England

Faculty of Anæsthetists—Dr G S W Organe has been elected dean of the faculty for the coming year, and Prof E A Pask vice-dean

Royal College of Physicians of Edinburgh

Dr Jessie Macgregor prize for medical women—An award of this prize, competition for which is open to women who are graduates in medicine of the University of Edinburgh or who have taken the Scottish triple qualification, will be made in November to the applicant who presents the best record of original work in the science of medicine Applications must reach the Convener of Trustees, Royal College of Physicians, 9, Queen Street, Edinburgh, 2, by Oct 31

British Association of Urological Surgeons

The following have been elected officers and members of council for 1958–59

President, Mr Arthur Jacobs, immediate past-president, Mr R H O B Robinson, vice-president, Mr Hugh Donovan, hon treasurer, Prof V W Dix, hon secretary, Mr J D Fergusson, hon editorial secretary, Mr N M Matheson, members of council, Mr F R Kilpatrick, Mr W S Mack, Mr T J Millin, Mr R A Mogg, Mr D S Poole-Wilson, Mr N L Shepperd, Mr J Swinney, and Mr D Innes Williams, and (ex officio) the president of the Section of Urology of the Royal Society of Medicine and the chairman of the editorial committee of the *British Journal of Urology*

International Congress on the Modern Educational Treatment of Deafness

This congress will be held at the University of Manchester from July 15 to 23 Further particulars may be had from Mr D M C Dale, department of education of the deaf, the University, Manchester, 13

British Medical Association

Dain Fund—During 1957–58 the Fund has spent £2300 in grants, helping 23 cases including 7 new ones Nearly every child needs help over a period of years, and, as school fees are mounting and the help required increases, subscribers are asked to continue their support and to enlist the support of others

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Dr J A Fraser Roberts has been elected president of the Royal Anthropological Society

Dr Brian MacMahon has been appointed professor of epidemiology at the Harvard School of Public Health

Dr Alex Comfort and Dr D S McLaren are among those who have received this year Ciba awards for research on the problems of ageing

A meeting of the Society for General Microbiology will be held in the University of Liverpool on Sept 18 and 19 Further particulars may be had from Dr B W Lacey, department of bacteriology, Westminster Medical School, London, S W 1

Caution—be Warned in Rhyme—Mr Edmund Quarry, the editor of *Better Health*, has for the past ten years offered his readers pills of good advice in the jam of light verse His good-natured admonishments have now been collected in a small book (London Hodgetts Pp 65 4*s* 6*d*) which he has illustrated himself

CORRIGENDUM *Billy Goes to Hospital*—We apologise to Prof R S Illingworth and to those readers who were perplexed by last week's reference (p 1399) to his article "on another page of this issue" Our note about the Guy's booklet was to have appeared with Professor Illingworth's paper, which will be published soon

Diary of the Week

JULY 6 TO 12

Sunday, 6th

UNIVERSITY COLLEGE HOSPITAL, Gower Street, W C 1
10 15 A M Dr H A Burt Backache, its Prevention and Treatment

Monday, 7th

UNIVERSITY OF LONDON
5 P M (St Mary's Hospital Medical School, Norfolk Place, W 2) Prof Gerrit Bras (Jamaica) Veno-occlusive Disease of the Liver

Tuesday, 8th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Sir Lindor Brown Mode of Action of Sympathetic Nerves (Bertram Louis Abrahams lecture)
INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W C 1
5 P M Dr David Gitlin (Boston) Plasma Protein Metabolism in the Nephrotic Syndrome
INSTITUTE OF PSYCHIATRY, *Maudsley Hospital, Denmark Hill*, S E 5
5 P M Prof George Rosen (New York) Social Stress and Mental Diseases in the 18th, 19th, and 20th Centuries

Wednesday, 9th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
2 P M Dr George Belyavin Serology of the Influenza Viruses

Thursday, 10th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Prof P B Medawar The Biology of Ageing (F E Williams lecture)

Appointments

MCARTHUR, MARY I, M B Edin, D P H assistant M O, South Buckinghamshire area
WILD, DAVID, M B Manc, D OBST assistant divisional M O, Eccles (near Manchester) area
WRIGHT, J T, D M Oxon, M R C P consultant physician, London Hospital, Whitechapel

East Anglian Regional Hospital Board

DAS, N, M B Calcutta, D T M & H, D G O registrar in obstetrics and gynæcology, West Norfolk and King's Lynn General Hospital
DOCKERY, PATRICIA J, M B Dubl, D C H pædiatric registrar, Ipswich and East Suffolk Hospital
GIBBON, R H, M B Cantab radiological registrar, Norfolk and Norwich Hospital
GIBSON, D S, M B Melb surgical registrar, West Suffolk General Hospital

Oxford Regional Hospital Board

CAREY, R W, M B Dubl, D O part-time consultant ophthalmologist, Oxford/Banbury area
MOSS JOHN M B Birm, D O part time consultant ophthalmologist, Aylesbury/High Wycombe area
PALMER J R, M B Lond, D P M assistant psychiatrist (S H M O) Fair Mile Hospital, near Wallingford, Berkshire

The Lancet · Saturday 12 July 1958

THE ROLE OF ENDOGENOUS PYROGEN IN THE GENESIS OF FEVER *

W Barry Wood, Jr
M D Johns Hopkins
PROFESSOR OF MICROBIOLOGY

From the Department of Microbiology, Johns Hopkins University School of Medicine and School of Hygiene and Public Health, Baltimore, Maryland

The view that fever and inflammation are intimately related is more than a hundred years old In 1851 Zimmermann[48] suggested that fever might be caused by products of inflammatory lesions His suggestion received prompt support from a number of investigators, who succeeded in preparing from purulent exudates a variety of extracts which, when injected intravenously, produced fever[13 19 24 45] In the light of subsequent evidence it is significant that at least some of these early preparations were relatively resistant to heat

Pyrexin

In 1943 Menkin[32] separated from inflammatory exudates a pyrogenic euglobulin fraction which he later named "pyrexin" It too was heat-stable, even when boiled, it retained its full activity[33] In this regard it resembled bacterial pyrogens[8] More recent studies have revealed that pyrexin has many of the other properties of pyrogenic bacterial endotoxins[10] Like them, it produces fever only after a relatively long latent period when injected intravenously, it causes an appreciable leucopenia after the injection, it induces a state of refractoriness, known as tolerance, when administered repeatedly†, and its pyrogenic effect is much depressed when it is injected into animals previously made tolerant to other bacterial pyrogens Indeed its resemblance to bacterial pyrogens is so striking that Menkin[34] concludes that pyrexin may be a "complex" of bacterial pyrogen with serum-globulin

Leucocytic Pyrogen

Five years after Menkin's report, a fever-producing substance with very different properties was extracted from polymorphonuclear leucocytes by Beeson[8] Unlike pyrexin and bacterial pyrogens, the leucocytic pyrogen was eventually found to have the following properties (1) it was relatively heat-labile[10], (2) it caused a briefer febrile response (after a relatively short latent period)[10], (3) it caused little, if any, post-injection leucopenia[10], (4) it was fully active in recipients tolerant to bacterial pyrogens[8], (5) it did not produce tolerance when repeatedly injected[10], and (6) it was, at least to some extent, species-specific in its action[36]

This last property is of particular interest in relation to Menkin's original experiments Whereas he demonstrated that pyrexin extracted from inflammatory exudates in dogs was pyrogenic to rabbits, Petersdorf and Bennett[36] find that the pyrogen contained in canine leucocytes is inactive in rabbits Clearly, leucocytic pyrogen and pyrexin are two different substances

The accompanying table shows that each of the characteristic properties of pyrexin is common not only to bacterial pyrogens but also to the toxic polysaccharides extracted chemically from normal tissues by Landy and Shear[30] In contrast, none of these properties is shared by leucocytic pyrogen

Transferable Pyrogen

In 1953 Grant and Whalen,[21] studying the pyrexial response of rabbits to typhoid vaccine, detected in their sera, as long as three hours after the injection of the vaccine, a component which produced fever when injected intravenously into a second set of rabbits Having shown that typhoid vaccine previously incubated with normal rabbit plasma caused the same kind of prompt response as that induced by the transferable pyrogen, they concluded that the latter was formed by an interaction of the originally injected bacterial endotoxin with the plasma

Two years later Atkins and Wood[1 2] showed that the transferable pyrogen detected by Grant and Whalen[21] was quite separate from bacterial endotoxin Whereas the endotoxin was rapidly cleared from the blood-stream, the transferable pyrogen persisted throughout the febrile response, and its concentration in the circulation was directly proportional to the intensity of the fever[2] The newly discovered factor appeared to be endogenous and was biologically indistinguishable from leucocytic pyrogen (see table)

COMPARATIVE PROPERTIES OF PYROGENS

Pyrogen	Stability to heat *	Relative length of latent period	Post-injection leucopenia	Activity when injected into tolerant recipients	Production of tolerance	Action on thermoregulatory centres when in circulation
Bacterial endotoxins[8]	Stable[8]	Long[8]	Marked[8]	Depressed[8]	Yes[8]	Indirect[8] †
Pyrexin[33]	Stable[33]	Long[10]	Marked[33]	Depressed[33]	Yes[10]	§
Chemically extracted tissue polysaccharides[30]	Stable[30]	Long[30]	Marked[30]	Depressed[30]	Yes[30]	§
Leucocytic pyrogen[8]	Unstable[10]	Short[10]	Slight or none[10]	Unaffected[10]	No[10]	Direct[27]
Pyrogen in circulation during endotoxin-induced pyrexia[2]	? ‡	Short[2]	Slight or none[2]	Unaffected[2]	No[21]	Direct[7]
Pyrogen in circulation during febrile phase of acute bacterial infections[21]	? ‡	Short[21]	§	Unaffected[21]	§	Direct[1]

* Exposure to 90 C for 30 minutes
† Action may be 'direct' when endotoxin is in spinal fluid.[28]
‡ No satisfactory method has been developed for testing heat-stability of pyrogen in presence of serum.[21]
§ Not yet tested.

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* The studies from the author's laboratory which are referred to in this article were supported by a grant from the Life Insurance Medical Research Fund They were made in collaboration with Elisha Atkins, M.D., of the department of medicine, Yale University School of Medicine, New Haven, Connecticut, and M Kenton King, M D, of the departments of medicine and preventive medicine, Washington University School of Medicine, St Louis, Missouri

† Menkin's (1955) finding that pyrexin, when given in large enough doses, does not produce tolerance, does not invalidate the earlier observation[19] that it does so when given in smaller doses It has been clearly established that tolerance to bacterial pyrogens may be wholly masked, if the doses used in the repeated injections are sufficiently large[38]

The lamp has been thoroughly tested It has been found particularly helpful in operations deep in the thorax, the abdomen, or the pelvis, it is usually best used in conjunction with normal overhead lighting, and sometimes only for quite short periods during an operation It has also found favour with ophthalmic surgeons, and it has been in constant use in casualty departments The spotlight is always in focus, is very bright, and is astonishingly easy to manœuvre

This spotlight may be obtained from Messrs Herbert Terry and Sons Ltd, Redditch, or their agents

University of London

The board of governors of Queen Charlotte's Hospital and the Chelsea Hospital for Women have set aside £50,000 of their endowment funds for the endowment of a chair of obstetrics and gynæcology at the Institute of Obstetrics and Gynæcology

University of Leeds

At recent examinations the following were successful

M B , Ch B—Margaret Barber, Pauline Bittner, Norman Carr, Frank Carter, Margaret E Coles, A J K Dore, M W Flowers, Gillian M Foster, R D Jackson, J N Lambton, P B Pickles, Stanley Sorkin, Freda M Tomlinson, B K Turnbull, R K Wright

D P M—John Blackburn, Margaret W Galley, Mary Jones, H B Kidd, J T Rose, Brian Ward

University of Liverpool

Dr K McCarthy and Dr K R Dumbell have been appointed senior lecturers in bacteriology, and Dr J L Braithwaite and Dr E W Macmillan senior lecturers in anatomy

University of Manchester

At a recent examination the following were successful

M B , Ch B—J W Aspinall, Roy Battye, F H Brindle, D B Brookes, J E Brooks, A L Buckley, Eric Charles, P J Cox, J S Cumming, Barry Deakin, B H Delany, G G Duckworth, R M Flinn, Joyce Harris, Roy Haworth, Patricia A Hegarty, Raymond Holmes, Alexander Hopkins, W H Isbister, Maria Z Kozubowska, R J Lawton, I P McEwan, A C Peterson, J D Rhodes, P H Roberts, Martin Ryan, Elizabeth M Spencer, Roy Statham, Garo Tahta, Peter Watson, J M Watts, B K Wignall, J D G Williams, S K Wood, P B Wrigglesworth

Queen's University, Belfast

Dr T K Marshall has been appointed to a lectureship in pathology (forensic medicine)

Royal College of Surgeons of England

Faculty of Anæsthetists—Dr G S W Organe has been elected dean of the faculty for the coming year, and Prof E A Pask vice-dean

Royal College of Physicians of Edinburgh

Dr Jessie Macgregor prize for medical women—An award of this prize, competition for which is open to women who are graduates in medicine of the University of Edinburgh or who have taken the Scottish triple qualification, will be made in November to the applicant who presents the best record of original work in the science of medicine Applications must reach the Convener of Trustees, Royal College of Physicians, 9, Queen Street, Edinburgh, 2, by Oct 31

British Association of Urological Surgeons

The following have been elected officers and members of council for 1958–59

President, Mr Arthur Jacobs, immediate past-president, Mr R H O B Robinson, vice-president, Mr Hugh Donovan, hon treasurer, Prof V W Dix, hon secretary, Mr J D Fergusson, hon editorial secretary, Mr N M Matheson, members of council, Mr F R Kilpatrick, Mr W S Mack, Mr T J Millin, Mr R A Mogg, Mr D S Poole-Wilson, Mr N L Shepperd, Mr J Swinney, and Mr D Innes Williams, and (ex officio) the president of the Section of Urology of the Royal Society of Medicine and the chairman of the editorial committee of the *British Journal of Urology*

International Congress on the Modern Educational Treatment of Deafness

This congress will be held at the University of Manchester from July 15 to 23 Further particulars may be had from Mr D M C Dale, department of education of the deaf, the University, Manchester, 13

British Medical Association

Dain Fund—During 1957–58 the Fund has spent £2300 in grants, helping 23 cases including 7 new ones Nearly every child needs help over a period of years, and, as school fees are mounting and the help required increases, subscribers are asked to continue their support and to enlist the support of others

Dr J A Fraser Roberts has been elected president of the Royal Anthropological Society

Dr Brian MacMahon has been appointed professor of epidemiology at the Harvard School of Public Health

Dr Alex Comfort and Dr D S McLaren are among those who have received this year Ciba awards for research on the problems of ageing

A meeting of the Society for General Microbiology will be held in the University of Liverpool on Sept 18 and 19 Further particulars may be had from Dr B W Lacey, department of bacteriology, Westminster Medical School, London, S W 1

Caution—be Warned in Rhyme—Mr Edmund Quarry, the editor of *Better Health*, has for the past ten years offered his readers pills of good advice in the jam of light verse His good-natured admonishments have now been collected in a small book (London Hodgetts Pp 65 4*s* 6*d*) which he has illustrated himself

CORRIGENDUM *Billy Goes to Hospital*—We apologise to Prof R S Illingworth and to those readers who were perplexed by last week's reference (p 1399) to his article "on another page of this issue" Our note about the Guy's booklet was to have appeared with Professor Illingworth's paper, which will be published soon

Diary of the Week

JULY 6 TO 12

Sunday, 6th

UNIVERSITY COLLEGE HOSPITAL, Gower Street, W C 1
10 15 A M Dr H A Burt Backache, its Prevention and Treatment

Monday, 7th

UNIVERSITY OF LONDON
5 P M (St Mary's Hospital Medical School, Norfolk Place, W 2) Prof Gerrit Bras (Jamaica) Veno-occlusive Disease of the Liver

Tuesday, 8th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Sir Lindor Brown Mode of Action of Sympathetic Nerves (Bertram Louis Abrahams lecture)
INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W C 1
5 P M Dr David Gitlin (Boston) Plasma Protein Metabolism in the Nephrotic Syndrome
INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S E 5
5 P M Prof George Rosen (New York) Social Stress and Mental Diseases in the 18th, 19th, and 20th Centuries

Wednesday, 9th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
2 P M Dr George Belyavin Serology of the Influenza Viruses

Thursday, 10th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Prof P B Medawar The Biology of Ageing (F E Williams lecture)

Appointments

MCARTHUR, MARY I, M B Edin, D P H assistant M O, South Buckinghamshire area
WILD, DAVID, M B Manc, D OBST assistant divisional M O, Eccles (near Manchester) area
WRIGHT, J T, D M Oxon, M R C P consultant physician, London Hospital, Whitechapel

East Anglian Regional Hospital Board

DAS, N, M B Calcutta, D T M & H, D G O registrar in obstetrics and gynæcology, West Norfolk and King's Lynn General Hospital
DOCKERY, PATRICIA J, M B Dubl, D C H pædiatric registrar, Ipswich and East Suffolk Hospital
GIBBON, R H, M B Cantab radiological registrar, Norfolk and Norwich Hospital
GIBSON, D S, M B Melb surgical registrar, West Suffolk General Hospital

Oxford Regional Hospital Board

CAREY, R W, M B Dubl, D O part time consultant ophthalmologist, Oxford/Banbury area
MOSS JOHN, M B Birm, D O part time consultant ophthalmologist, Aylesbury/High Wycombe area
PALMER, J R, M B Lond, D P M assistant psychiatrist (S H M O) Fair Mile Hospital, near Wallingford, Berkshire

The Lancet · Saturday 12 July 1958

THE ROLE OF ENDOGENOUS PYROGEN IN THE GENESIS OF FEVER*

W Barry Wood, Jr
M D Johns Hopkins
PROFESSOR OF MICROBIOLOGY

From the Department of Microbiology, Johns Hopkins University School of Medicine and School of Hygiene and Public Health, Baltimore, Maryland

The view that fever and inflammation are intimately related is more than a hundred years old In 1851 Zimmermann [48] suggested that fever might be caused by products of inflammatory lesions His suggestion received prompt support from a number of investigators, who succeeded in preparing from purulent exudates a variety of extracts which, when injected intravenously, produced fever [13 19 24 45] In the light of subsequent evidence it is significant that at least some of these early preparations were relatively resistant to heat.

Pyrexin

In 1943 Menkin [32] separated from inflammatory exudates a pyrogenic euglobulin fraction which he later named "pyrexin" It too was heat-stable, even when boiled, it retained its full activity [33] In this regard it resembled bacterial pyrogens [8] More recent studies have revealed that pyrexin has many of the other properties of pyrogenic bacterial endotoxins [10] Like them, it produces fever only after a relatively long latent period when injected intravenously, it causes an appreciable leucopenia after the injection, it induces a state of refractoriness, known as tolerance, when administered repeatedly†; and its pyrogenic effect is much depressed when it is injected into animals previously made tolerant to other bacterial pyrogens Indeed its resemblance to bacterial pyrogens is so striking that Menkin [34] concludes that pyrexin may be a "complex" of bacterial pyrogen with serum-globulin

Leucocytic Pyrogen

Five years after Menkin's report, a fever-producing substance with very different properties was extracted from polymorphonuclear leucocytes by Beeson [3] Unlike pyrexin and bacterial pyrogens, the leucocytic pyrogen was eventually found to have the following properties (1) it was relatively heat-labile [10], (2) it caused a briefer febrile response (after a relatively short latent period) [10] (3) it caused little, if any, post-injection leucopenia [10] (4) it was fully active in recipients tolerant to bacterial pyrogens [6], (5) it did not produce tolerance when repeatedly injected [10], and (6) it was, at least to some extent, species-specific in its action.[36]

This last property is of particular interest in relation to Menkin's original experiments Whereas he demonstrated that pyrexin extracted from inflammatory exudates in dogs was pyrogenic to rabbits, Petersdorf and Bennett [36] find that the pyrogen contained in canine leucocytes is inactive in rabbits Clearly, leucocytic pyrogen and pyrexin are two different substances

The accompanying table shows that each of the characteristic properties of pyrexin is common not only to bacterial pyrogens but also to the toxic polysaccharides extracted chemically from normal tissues by Landy and Shear [30] In contrast, none of these properties is shared by leucocytic pyrogen

Transferable Pyrogen

In 1953 Grant and Whalen,[21] studying the pyrexial response of rabbits to typhoid vaccine, detected in their sera, as long as three hours after the injection of the vaccine, a component which produced fever when injected intravenously into a second set of rabbits Having shown that typhoid vaccine previously incubated with normal rabbit plasma caused the same kind of prompt response as that induced by the transferable pyrogen, they concluded that the latter was formed by an interaction of the originally injected bacterial endotoxin with the plasma

Two years later Atkins and Wood [1 2] showed that the transferable pyrogen detected by Grant and Whalen [21] was quite separate from bacterial endotoxin Whereas the endotoxin was rapidly cleared from the blood-stream, the transferable pyrogen persisted throughout the febrile response, and its concentration in the circulation was directly proportional to the intensity of the fever [2] The newly discovered factor appeared to be endogenous and was biologically indistinguishable from leucocytic pyrogen (see table)

COMPARATIVE PROPERTIES OF PYROGENS

Pyrogen	Stability to heat *	Relative length of latent period	Post-injection leucopenia	Activity when injected into tolerant recipients	Production of tolerance	Action on thermoregulatory centres when in circulator
Bacterial endotoxins [8]	Stable [8]	Long [8]	Marked [8]	Depressed [8]	Yes [8]	Indirect [2] †
Pyrexin [32]	Stable [33]	Long [10]	Marked [33]	Depressed [18]	Yes [10]	§
Chemically extracted tissue polysaccharides [30]	Stable [30]	Long [30]	Marked [30]	Depressed [30]	Yes [30]	§
Leucocytic pyrogen [3]	Unstable [10]	Short [10]	Slight or none [10]	Unaffected [15]	No [10]	Direct
Pyrogen in circulation during endotoxin-induced pyrexia [2]	? ‡	Short [2]	Slight or none [2]	Unaffected [2]	No [39]	Direct [7]
Pyrogen in circulation during febrile phase of acute bacterial infections [28]	? ‡	Short [1]	§	Unaffected [28]	§	Direct [28]

* Exposure to 90 C for 30 minutes
† Action may be 'direct' when endotoxin is in spinal fluid.[3]
‡ No satisfactory method has been developed for testing heat-stability of pyrogen in presence of serum.[23]
§ Not yet tested.

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* The studies from the author's laboratory which are referred to in this article were supported by a grant from the Life Insurance Medical Research Fund They were made in collaboration with Elisha Atkins, M.D, of the department of medicine, Yale University School of Medicine, New Haven Connecticut, and M Kenton King, M D, of the departments of medicine and preventive medicine, Washington University School of Medicine, St Louis, Missouri

† Menkin's (1955) finding that pyrexin, when given in large enough doses, does not produce tolerance, does not invalidate the earlier observation [10] that it does so when given in smaller doses It has been clearly established that tolerance to bacterial pyrogens may be wholly masked, if the doses used in the repeated injections are sufficiently large.[23]

Cell-injury Hypothesis

These findings, taken in conjunction with the fact that bacterial endotoxins have both an affinity [15] and a toxicity [14, 29] for leucocytes, led to the suggestion that endotoxin-induced fever is due to the activation of thermoregulatory centres of the brain by circulating endogenous pyrogen released from leucocytes injured by the endotoxin [2] The relatively long latent period and the post-injection leucopenia, which are regularly observed in endotoxin fever,[8] appear to be in keeping with this hypothesis Recently, Bennett, Petersdorf, and Keene [12] have reported that the formation of circulating endogenous pyrogen, which follows the intravenous injection of endotoxin, is greatly depressed in animals previously made leucopenic with nitrogen mustard This finding also supports the suggestion that the endogenous pyrogen is of leucocytic origin

Possible Direct Action of Endotoxin

Certain other facts relating to endotoxin-induced fever, however, have led Bennett and his co-workers [5, 12, 38] to question the validity of this " cell-injury theory " They have justifiably emphasised that a fever-producing factor indistinguishable from leucocytic pyrogen is present in virtually agranulocytic exudates obtained from rabbits made leucopenic with nitrogen mustard [10] They have also shown that such leucopenic rabbits exhibit the usual febrile response to intravenously injected endotoxins,[11] even though circulating endogenous pyrogen is not detected in their blood-streams [12, 37] Furthermore they have shown by ingenious experiments that endotoxin injected intrathecally in minute amounts promptly causes pyrexia [25], that it does not cause tolerance if given repeatedly by this route [25], and that, if given intravenously in sufficiently large amounts, it will " spill over " into the spinal fluid [12] Having thus apparently dissociated the febrile response from the presence of circulating endogenous pyrogen, and having demonstrated that endotoxin in the spinal fluid is highly pyrogenic, they have postulated that the endotoxin itself may play a direct role in causing the fever [12, 38]

As mentioned elsewhere,[27, 28] these observations relating specifically to endotoxin fever must be interpreted with caution The evidence that endotoxin when introduced into the subarachnoid space will cause fever, apparently by acting on the central nervous system, is certainly conclusive That intrathecal endotoxin should have this effect is not surprising in view of the well-known sensitivity of the thermoregulatory centres to noxious stimuli [41] However, it should be emphasised that, after the intravenous injection of endotoxin, an apparent dissociation of the fever and the presence of circulating endogenous pyrogen has been achieved only by injecting relatively large doses of endotoxin under conditions in which the production of endogenous pyrogen is known to be depressed—i e , in the presence of either tolerance or profound leucopenia [12, 38] Furthermore, the failure to demonstrate circulating endogenous pyrogen by the passive transfer technique [1] does not necessarily indicate that it is absent, for the test, as usually applied, is capable of detecting only relatively large amounts of the endogenous factor [26] Sufficient endogenous pyrogen, for example, may be present in the blood of the endotoxin-injected (donor) animal to cause it to have fever, even though the amount transferred to a second (recipient) animal is insufficient to produce a febrile response Although in special circumstances intravenously injected endotoxin, given in sufficient amount, may reach the spinal fluid and thus initiate pyrexia,[12, 38] the data so far obtained do not negate the original observation that in normal animals capable of producing full amounts of endogenous pyrogen, the fever induced by moderate intravenous doses of endotoxin is directly related to the concentration of endogenous pyrogen in the blood-stream [2]

Pyrogenic Tissue Polysaccharides

The isolation of pyrogenic polysaccharides from various normal tissues by Landy and Shear [30] raises the additional question whether these substances may not somehow be involved in the production of fever At present it can only be stated that, since the biological properties of bacterial pyrogens and of the tissue polysaccharides have been shown to be the same [30] (see table), all the arguments against the direct action of the former pertain also to the latter If for no other reason than that they cause tolerance, it seems unlikely that the tissue polysaccharides, at least in the form isolated by Landy and Shear,[30] are directly responsible for natural pyrexia Were the causal pyrogen in the circulation capable of producing tolerance, pyrexia due to systemic disease could not be expected to be fully sustained for more than a few days It is conceivable, however, that tissue polysaccharides may eventually be shown to be released during cellular injury and, when so released, to cause the production of endogenous pyrogen There is as yet no evidence either for or against this interesting possibility

Source, and Site of Action of Endogenous Pyrogen

While the above-mentioned investigations of Bennett et al were in progress, further studies were undertaken relating to the source and the site of action of endogenous pyrogen Polymorphonuclear leucocytes were found to be the principal source of endogenous pyrogen in granulocytic exudates and were observed to discharge their pyrogenic component into the surrounding medium while still motile and apparently otherwise functionally intact [26] Both the endogenous pyrogen derived from leucocytic exudates and that present in the serum during endotoxin-induced fever were also found to exert their pyrogenic effects, when introduced into the circulation, by acting directly on the thermoregulatory centres of the brain [27] Circulating bacterial (exogenous) pyrogen, on the other hand, was shown to act by a different and less direct mechanism [27]

"Natural Fever" Models

Because both endogenous and exogenous pyrogens may, in certain circumstances, act on the cerebral centres to cause endotoxin-induced fever, this widely used experimental model is not entirely satisfactory for studying the pathogenesis of fever in general [27] Not only is it a relatively artificial model involving the injection of toxic foreign substances, but also it is characterised by certain features which appear to have no counterpart in naturally occurring pyrexia—e g , tolerance [8] Hence, studies must be extended to other experimental models, designed to simulate more closely the conditions of naturally occurring pyrexia Two such models have recently been investigated

In 1956 Bennett [7] reported extensive investigation of the fever of experimental pneumococcal peritonitis in rabbits During the febrile phase of the infection he found, in both the peritoneal exudate and the thoracic-duct lymph, a heat-labile substance which appeared to be identical with leucocytic pyrogen Its presence at both sites correlated closely with the animal's fever When defervescence was produced by penicillin therapy, the pyrogen was no longer detected in the exudate Although, in the latter circumstances, leucocytes were still plentiful in the peritoneal exudate, control of the infection apparently removed the stimulus which previously had caused the production of endogenous pyrogen The ability of the blood-stream to rid itself promptly of intravenously injected leucocytic pyrogen had already been established in an earlier study [6] Despite these important and highly suggestive findings, Bennett was unable to demonstrate the fever-producing factor in the blood-stream during the active infection Accordingly he was forced to conclude that the possible causal relationship between the fever and the endogenous pyrogen in the exudate and lymph had not been established

The demonstration of circulating pyrogen in such an experimental model is obviously crucial [6 39 42 46 47] A concerted attempt was therefore made to detect its presence at the height of the febrile phase of the infection When a passive-transfer method was used, in which considerably larger volumes of serum were employed than had been tested by Bennett, a pyrogen similar to that noted in the pneumococcal exudate and lymph was found to be present in the blood-stream [28] The transferable factor in the circulation was also shown to act directly on the thermoregulatory centres [28] Since the endogenous pyrogen in acute granulocytic exudates has been shown to come from polymorphonuclear leucocytes,[26] it now appears to be established beyond reasonable doubt that the fever of pneumococcal peritonitis in rabbits is caused by a circulating endogenous pyrogen produced by the polymorphonuclear leucocytes in the peritoneal exudate and carried to the blood-stream via lymphatic channels emptying into the thoracic duct.[25]

Similar results were obtained with a second experimental model—i e., one involving acute streptococcal cellulitis During the febrile phase of this infection also, an apparently identical endogenous pyrogen has been demonstrated in the blood-stream.[28]

In spite of the evidence provided by these latest experiments, the question may still be raised whether bacterial pyrogens do not play at least a secondary role in the production of pyrexia caused by experimental infections In pneumococcal peritonitis this possibility seems highly unlikely for the following reasons

(1) No bacterial pyrogen has ever been detected in pneumococcal cultures [7]

(2) The pyrogen detected by Bennett in the peritoneal exudate and thoracic-duct lymph was completely inactivated by being heated at 90°C for 30 minutes, did not produce tolerance when repeatedly injected, and was equally active in tolerant and normal recipients [7] In short, no heat-stable component compatible with a bacterial pyrogen was detected in either the exudate or the lymph.

(3) The factor found in the blood-stream was unlike bacterial pyrogen in that (*a*) its activity was the same in normal and tolerant recipients, and (*b*) its pyrogenicity was due to a direct effect on the thermoregulatory centres of the brain.[28]

(4) Relatively prolonged pneumococcal infections (6–9 days) did not induce tolerance to pyrogen,[4] thus virtually eliminating the possibility that a circulating bacterial pyrogen is involved in the pathogenesis of pneumococcal fever

The fact that bacterial endotoxins are active in minute quantities when injected intrathecally [25] suggests that pyrogenic products of the invading pneumococci might gain access to the subarachnoid space and thus contribute to the fever This possibility also appears to be excluded, since bacterial pyrogen was not detected in pneumococcal cultures or in the peritoneal exudate, the thoracic-duct lymph, or the blood-stream,[26 30] it is inconceivable that it could be present in the spinal fluid

In experimental streptococcal cellulitis the situation is complicated by the fact that a bacterial pyrogen can be extracted from β-hæmolytic streptococcal cells [44] However, the endotoxic activity of streptococcal extracts is relatively low,[44] and in this infection the organisms do not invade the blood-stream [28] Here again the circulating pyrogen which appears to cause the fever produces a more rapid febrile response than do bacterial pyrogens Furthermore, unlike bacterial pyrogen, it is uninfluenced by tolerance and acts directly on the central nervous system via the circulation [25]

Even in experimental infections caused by *Escherichia coli*, which is known to possess a powerful pyrogenic endotoxin, there is at present no evidence that the endotoxin is directly involved in the production of fever On the contrary, *Esch coli* infections of 7 or 8 days' duration, like pneumococcal infections, do not produce tolerance to bacterial pyrogens [4] Were the endotoxin to reach the spinal fluid in extracranial *Esch coli* infections, it would still have to traverse the blood-stream In so doing it would certainly be expected to cause some degree of pyrogen tolerance

Thus the conclusion appears justified that the fever of most, if not all, acute bacterial infections which give rise to predominantly granulocytic exudates and do not directly involve the central nervous system are caused by a common factor—i e., a circulating endogenous pyrogen derived from polymorphonuclear leucocytes and analogous to the bloodborne substance found in the sera of rabbits with pneumococcal peritonitis and streptococcal cellulitis [28]

The further possibility that similar circulating endogenous pyrogens, derived from leucocytes or other inflammatory cells, may cause an even wider variety of pyrexia is suggested by the fact that inflammation is common to many pyrexial states, including those resulting from viral infections, vascular lesions, hypersensitivity reactions, and neoplastic diseases [46] Pertinent to this more general hypothesis is the recent observation of Atkins [2] that the febrile response to intravenous injection of influenzal virus is directly related to the presence of a circulating endogenous pyrogen which is indistinguishable from leucocytic pyrogen Whether this newly identified factor is derived from polymorphonuclear leucocytes or from some other cellular source remains to be determined Equally important is Atkins' demonstration (personal communication) of a similar substance in the blood-stream of animals with fever induced by tuberculin hypersensitivity [43] Both these findings, together with those already mentioned relating to pneumococcal and streptococcal infections,[28] support the general theory that endogenous pyrogens derived from inflammatory exudates play a central role in the pathogenesis of many forms of fever

Studies in man [17 20 42] further support this concept Of particular significance is the fact that human serum and plasma have been shown to inactivate bacterial endotoxin [20 22 23‡] This inactivation may be related to the release of phosphorus from the endotoxin molecule [40] When, however, endotoxin is added to human whole blood or to plasma containing leucocytes, incubation for 3 hours results in the formation of a pyrogenic substance which apparently possesses all the biological properties of endogenous pyrogen [42] Since leucocytes are necessary in the system for production of the pyrogen,[17] and since its properties are indistinguishable from those of leucocytic pyrogen,[42] the inference may be drawn that the pyrogen is produced by the leucocytes A difference from the observations made with rabbit leucocytes [26] is that easily demonstrable amounts of the human endogenous pyrogen have been obtained only when the leucocytes have been exposed to the injurious action of endotoxin [39] This difference, however, may be merely quantitative

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‡ Endotoxin is also inactivated by rabbit serum when incubated at 37 C for more than a few hours [16]

The term “ endogenous pyrogen ” used in this and previous reports [1 2 26–28 46 47] refers to fever-producing substances which are apparently derived from sources within the body Clearly, leucocytic pyrogen [26 42] fits this definition, as do the pyrogenic factors contained in the blood-streams of rabbits with pyrexia caused either by injections of typhoid vaccine [1 2] § or by active pneumococcal and streptococcal infections [28] Unfortunately the same term has been applied by Grant and Whalen [21] to the pyrogenic factor which results from the interaction of bacterial pyrogens and serum Although its use to designate the pyrogen-serum product is justifiable on the grounds that the interaction may occur in the circulation, the resulting pyrogenic factor has been shown to form rapidly in vitro [16] and obviously involves a component which was originally exogenous For these reasons, to avoid confusion, it appears preferable to call the bacterial pyrogen-serum substance by another name The pyrogenic tissue polysaccharides of Landy and Shear [30] also qualify by definition as “ endogenous ”, but they were obtained only by relatively drastic procedures of chemical extraction [30] As emphasised by Landy and Shear, the extracted polysaccharides appear to be active “ only when they are released from their native state of firm combination with other cellular components ”,[30] and there is no evidence that they act directly as pyrogens in the intact host, even under conditions of disease

The endogenous pyrogens, as here defined, are biologically indistinguishable from leucocytic pyrogen (see table) Indeed there are numerous reasons, already reviewed, for believing that the circulating endogenous factor which appears to cause the fever of acute bacterial infections,[28] and that present in the blood during endotoxin-induced fever,[1 2] are both derived from polymorphonuclear leucocytes [26] All attempts to demonstrate similar endogenous pyrogens in saline extracts of other body cells have so far failed [5 9] It is still possible, however, that cells other than granulocytes can produce endogenous pyrogen If these cells could be identified, the fever seen in agranulocytosis and in diseases in which polymorphonuclear leucocytes do not appear to play a prominent role—e g , granulomata and viral infections—might be more readily explained On the other hand, it is not inconceivable that, even in these situations, enough leucocytes are affected in the vast extravascular granulocytic stores of the body [31] to explain the release of endogenous pyrogen Further experimental studies are needed to clarify these points

Chemistry

Since it is evident that leucocytic pyrogen is at least one of the endogenous factors directly responsible for fever, its chemical identity is of great interest Besides being inactivated when heated to 90°C for 30 minutes (at pH 7 2), leucocytic pyrogen is known to be non-dialysable through ‘ Cellophane ’ It has also been reported to be resistant to the actions of trypsin, chymotrypsin, and ribonuclease, and to be unaffected by pH changes ranging from 2 0 to 10 5 Significant pyrogenicity has been demonstrated in preparations containing 0 76 mg of protein and 0 054 mg of polysaccharide [10] Clearly, additional chemical data are needed, and studies designed to procure them are in progress

Summary

There is now strong experimental evidence that endogenous pyrogen derived from polymorphonuclear leucocytes in inflammatory exudates plays a central role in the pathogenesis of many kinds of fever Leucocytes in granulocytic exudates release the endogenous pyrogen into the surrounding medium while still functionally active.

During the febrile phase of experimental pneumococcal peritonitis the pyrogen has been found not only in the peritoneal exudate and the thoracic-duct lymph but also in the blood-stream

An endogenous pyrogen indistinguishable from leucocytic pyrogen has likewise been detected in the sera of rabbits with pyrexia resulting from acute streptococcal cellulitis, from tuberculin hypersensitivity, and from the intravenous injection of typhoid vaccine and of influenzal virus

This recently identified circulating factor acts directly on the thermoregulatory centres of the brain

Its biological properties differ distinctly from those of bacterial pyrogens, pyrexin, and the pyrogenic polysaccharides which can be chemically extracted from normal tissues None of the latter appears to be the direct cause of the fever seen in extracranial bacterial infections

Despite the progress achieved in elucidating the pathogenesis of fever, two major problems remain unsolved (1) the chemical identity of leucocytic pyrogen, and (2) the possibility that cells other than polymorphonuclear leucocytes may be able to elaborate a similar, if not identical, fever-producing factor

REFERENCES

1 Atkins, E , Wood, W B , Jr (1955a) *J exp Med* 101, 519
2 — — (1955b) *ibid* 102, 499
2a — Huang, W C (1958) *ibid* 107, 383
3 Beeson, P B (1948) *J clin Invest* 27, 524
4 Bennett, I L , Jr (1948) *J exp Med* 88, 267
5 — (1956a) *Bull Johns Hopk Hosp* 98, 1
6 — (1956b) *ibid* p 7
7 — (1956c) *ibid* p 216
8 — Beeson, P B (1950) *Medicine, Baltimore,* 29, 365
9 — — (1953a) *J exp Med* 98, 477
10 — — (1953b) *ibid* p 493
11 — Cluff, L E (1952) *Proc Soc exp Biol , N Y* 81, 304
12 — Petersdorf, R G , Keene, W R (1957) *Trans Ass Amer Phycns,* 70, 64
13 Bergmann, E. (1868) *St Petersb med Z* 15, 16
14 Berthrong, M , Cluff, L E (1953) *J exp Med* 98, 331
15 Braude, A I , Carey, F J , Zalesky, M (1955) *J clin Invest* 34, 858
16 Cluff, L., Bennett I L. Jr (1957) *Bull Johns Hopk Hosp* 101, 281
17 Cranston, W I , Goodale, F , Jr , Snell, E S , Wendt, F (1956) *Clin Sci* 15, 219
18 Farr, R S , Clark, S L., Jr , Proffitt, J E (1953) *Nat med Res Inst Rep*
19 Frese, J B (1866) Inaugural dissertation, University of Dorpat
20 Goodale, F., Jr , Snell, E S , Wendt, F , Cranston, W I (1956) *Clin Sci* 15, 491
21 Grant, R., Whalen W J (1953) *Amer J Physiol* 173, 47
22 Hegemann, F (1954a) *Z ImmunForsch* 111, 202.
23 — (1954b) *ibid* p 213
24 Hufschmidt, von E (1865) *Arch klin Chir* 6 382
25 Keene, W R (1956) *Bull Johns Hopk Hosp* 99, 103
26 King, M K., Wood, W B , Jr (1958a) *J exp Med* 107, 279
27 — — (1958b) *ibid* p 291
28 — — (1958c) *ibid* p 305
29 Kirby, G P , Barrett, I A , Jr (1954) *J clin Invest* 33, 725

references continued at foot of next column

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§ Endogenous pyrogen is easily demonstrable in the sera of such animals 2 hours after inoculation of the vaccine, at which time the bacterial pyrogen contained in the originally injected vaccine is no longer detectable in the circulation [2]

GROSS DIGITAL CLUBBING AND EXOPHTHALMIC OPHTHALMOPLEGIA IN THYROID DISORDERS

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It is a sobering thought that the pathogenesis of such a common and easily recognisable physical sign as clubbing of the fingers should still not be fully understood As early as the 5th century B C , curving of the finger nails in a woman with an empyema was recorded by Hippocrates Yet the reason why digital clubbing occurs remains a matter of conjecture and controversy

Clubbing of the fingers and hypertrophic pulmonary osteoarthropathy are now generally ascribed either to peripheral anoxia or to a disturbance of endocrine function rather than to the "toxins" of earlier workers (*Lancet* 1955) Nevertheless very few textbooks on clinical medicine or on endocrinology mention the association of finger clubbing with disorders of the endocrine glands For example, although there are some isolated references to the fact that acropachy may, on rare occasions, occur in postoperative myxœdema, far greater emphasis is laid on the fact that the nails usually become atrophic and unduly brittle in this condition

Digital Clubbing, Exophthalmic Ophthalmoplegia, and Hypothyroidism

Thomas (1933) reported a man, aged 22, who first observed curving of his finger nails about eight months after partial thyroidectomy for exophthalmic goitre Sixteen months later he was mildly myxœdematous and had œdema of the eyelids There is no indication in the case-report whether the exophthalmos had progressed or diplopia had developed Extreme clubbing of the fingers and enlargement of the hands and wrists were present The toenails were normal Radiography revealed tufting of the terminal phalanges and much subperiosteal formation of new bone, the sella turcica was normal

Cushing (1937) described a further case A negro, aged 37, first noticed that the tips of his fingers were becoming swollen eight months after subtotal thyroidectomy He had severe digital clubbing, and radiography showed generalised hypertrophic pulmonary osteoarthropathy affecting his long bones and metacarpals His basal metabolic rate was −24% compared with +55% before operation As in the previous case, nothing is said about whether ophthalmoplegia had complicated the pre-existing exophthalmos

Rynearson and Sacasa (1941) reported a man, aged 43, who became hypothyroid and developed clubbing of his fingers six weeks after partial thyroidectomy for thyrotoxicosis Two years after the operation his exophthalmos had increased and he had brawny irregular non-pitting œdema of the lower half of his legs His basal metabolic rate was −13%, and radiography showed subperiosteal thickening of his phalanges

Greene (1951) described a man, aged 74, with hypothyroidism, malignant exophthalmos, and gross clubbing of the fingers and toes, who at the age of 56 in 1932 had an enlarged thyroid gland, exophthalmos, an enlarged heart, and chronic bronchitis He had no digital tremor or tachycardia After treatment with potassium iodide the goitre disappeared At this time his fingers were clubbed but, according to his relations, this only became severe seventeen years later, when progressive exophthalmos appeared He also had pretibial thickening of his skin Radiography of his chest showed emphysema, a bronchogram was normal Radiography of his skull showed no abnormality, radiography of his hands and feet revealed the formation of new bone along the shafts of his phalanges and metacarpals

This man died in 1951 A necropsy was done by Dr A B Bratton, and I am indebted to Dr Greene for sending me full details of the hitherto unpublished necropsy findings In summary, there were considerable hypertrophy of the left ventricle, œdema of the lungs, and emphysema A cystic adenoma was present in the left lobe of the thyroid gland, and microscopy revealed lymphocytic infiltration, massive fibrosis, and scanty colloid in the small residual nodules of thyroid epithelium The suprarenal glands had abundant lipoid in the cortex and considerable lymphocytic infiltration of the medulla There was an eosinophil chromophil adenoma of the anterior lobe of the pituitary gland

Inch and Rolland (1953) reported 2 cases in which pretibial myxœdema and gross digital clubbing were associated with exophthalmic ophthalmoplegia One case was in a woman who developed an exophthalmic goitre at the age of 36 Within nine months of partial thyroidectomy she had signs of hypothyroidism, ophthalmoplegia, pretibial myxœdema, and finger clubbing The other case was in a man who became thyrotoxic at the age of 20 After X-irradiation of the thyroid gland he became euthyroid and developed exophthalmos with mild ophthalmoplegia He was first seen by Inch and Rolland nineteen years later with considerable exophthalmos, some ophthalmoplegia, pretibial myxœdema, and gross finger clubbing The patient did not know when the clubbing had begun to appear

Analysis of these 6 case-reports reveals that the clinical features common to all were digital clubbing and exophthalmos 5 patients were hypothyroid, and 1 was euthyroid This hypothyroid or euthyroid state followed partial thyroidectomy or X-irradiation of the thyroid gland for thyrotoxicosis in 5 patients In 1 case myxœdema was first noticed about seventeen years after the goitre had disappeared after treatment with potassium iodide

Exophthalmic ophthalmoplegia was present in 4 cases, whereas in 2 (Thomas 1933, Cushing 1937) it is not said whether the pre-existing exophthalmos had increased or diplopia had developed In 4 patients digital clubbing came on between six weeks and nine months after either partial thyroidectomy or X-irradiation of the thyroid gland and closely followed the symptoms of hypothyroidism In 1 case the patient did not know when the clubbing had first appeared In the other case, although the clubbing had appeared before the goitre had been treated with potassium iodide, it had only become severe seventeen years later, when hypothyroid symptoms and malignant exophthalmos had developed Pretibial myxœdema was observed in 3 of the 6 cases

A further case is now reported

Case-reports

Case 1 —An engine driver, aged 56, was referred to the Bristol Eye Hospital in October, 1957, with three months' history of increasing prominence of his eyes For three weeks

PROF WOODS REFERENCES—*continued*

30 Landy, M , Shear, M J (1957) *J exp Med* 106, 77
31 Lawrence J S (1955) *J Amer med Ass* 157, 1212
32 Menkin, V (1943) *Arch Path* 36, 269
33 — (1945) *ibid* 39, 28
34 — (1955) *J Lab clin Med* 46, 423
35 Petersdorf, R. G , Bennett, I L., Jr (1957a) *Bull Johns Hopk Hosp* 100, 197
36 — — (1957b) *ibid* p 277
37 — — (1957c) *J exp Med* 106, 293
38 — Keene, W R , Bennett, I L., Jr (1957) *ibid* p 787
39 Pickering, G (1958) *Lancet*, i 59
40 Rowley, D , Howard J G Jenkin, C R. (1956) *ibid* i, 366
41 Selle W A (1952) Body Temperature Springfield Ill
42 Snell, E S , Goodale, F , Jr , Wendt, F , Cranston, W L (1957) *Clin Sci* 16 615
43 Stetson, C A Jr (1955) *J exp Med* 101, 421
44 — (1956) *ibid* 104 921
45 Weber, O (1864) *Dtsch klin* 16, 461, 17, 13
46 Wood W B Jr (1955) see *Amer J Med* 18, 351
47 — (1957) *Sci Amer* , 196, 62
48 Zimmermann, G (1851) *Arch Path Ther* 1, 1

he had had progressive swelling of his left upper eyelid and watering of the eye During the preceding seven days he had had pain in his left eye and photophobia and could not close his eye completely In 1929, at the age of 28, subtotal thyroidectomy followed by X-irradiation of the thyroid gland were undertaken for thyrotoxicosis of some eleven months' duration The hospital records state that after this treatment the exophthalmos regressed somewhat and the patient regained his previous weight For four months before be was seen at the Bristol Eye Hospital he had felt tired and been unduly sensitive to cold, and his skin had become rough and dry and his voice a little husky, and he was constipated There was no apparent impairment of memory or of power to concentrate For about twenty years up to the time of admission he had been driving a main-line express train

On examination his speech was a little slow and slurred and his voice low-pitched He had coarse features, a dry scaly skin, dry hair, and a puffy face No circumscribed or pretibial myxœdema was found Gross clubbing of his fingers and toes was present (fig 1) There was neither pain nor swelling of his ankles, feet, or wrists Marked bilateral exophthalmos (exophthalmometer right eye 29 mm , left eye 28 mm *) was present Œdema and inflammation of his periorbital tissues and the infracorneal conjunctiva were severe His left eye was lagophthalmic, with eversion of the lower lid, exposing œdematous conjunctiva and producing epiphora (fig 2) He had no diplopia, but he had difficulty in looking upwards His visual acuity was right 6/9, left 6/18, his ocular fundi and visual fields were normal His cardiovascular system, chest, and abdomen revealed no abnormal physical signs

Investigations and follow-up examination—During his stay in hospital the patient's temperature was 96–98°F and pulse-rate 60–70 Blood-counts and liver-function tests were normal, his plasma-cholesterol level was 280 mg per 100 ml

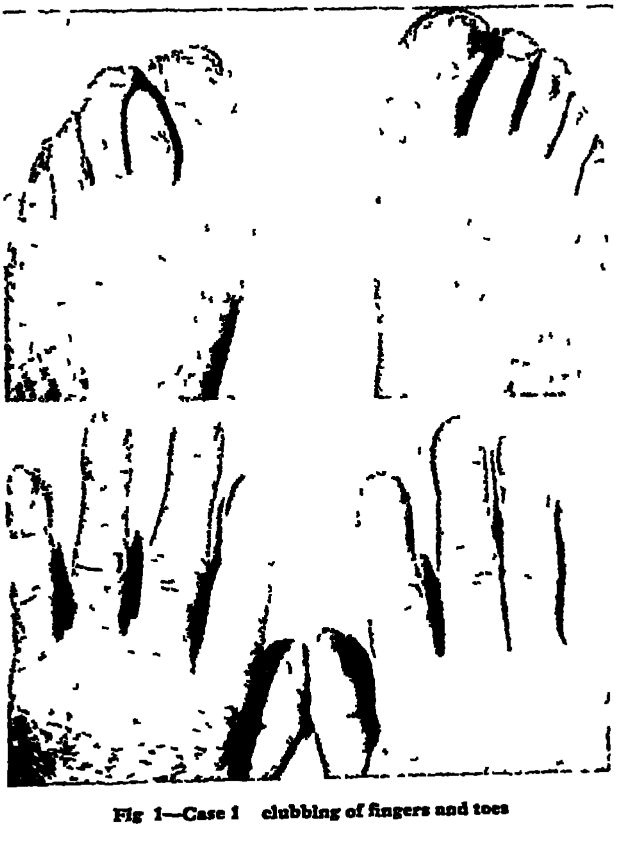

Fig 1—Case 1 clubbing of fingers and toes

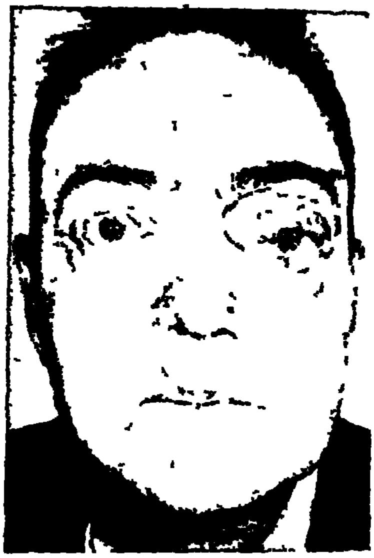

Fig 2—Case 1 malignant exophthalmos Left lateral and central and right lateral tarsorrhaphies had been done as emergency measure

Electrocardiography revealed flattening of the T waves in all leads Radiography of his chest showed fibrotic changes in the anterior segment of the right upper lobe and bilateral basal emphysema Bronchography showed all the main segmental bronchi in both lungs and no evidence of bronchiectasis Radiography of his skull, hands, and long bones was normal, but there was periosteal new bone on the medial aspects of both first metatarsals (Dr J H Middlemiss) Radioactive-iodine estimations showed that at four hours the total uptake was as low as 9% of the dose, and at forty-eight hours the protein-bound ^{131}I level in the plasma was 0 13% of the dose per litre, the values obtained being consistent with the clinical diagnosis of myxœdema A left central and lateral tarsorrhaphy and a right lateral tarsorrhaphy were done as an emergency measure, and a course of X-irradiation to the orbits has now been given

Comment—There was no history or clinical evidence of pulmonary, cardiac, hepatic, or intestinal disease in this patient and no family history of clubbing of the fingers Although the plain radiographs of his chest showed fibrotic changes in the anterior segment of the right upper lobe, bronchography showed no bronchiectasis The patient and his wife both thought that the clubbing of his fingers had been present for only three or four months In this patient, therefore, there was a definite association between the onset of digital clubbing, exophthalmic ophthalmoplegia, and clinical manifestations of hypothyroidism

Digital Clubbing, Exophthalmic *Ophthalmoplegia*, and Thyrotoxicosis

Although it is well known that trophic disturbances leading to koilonychia may develop in thyrotoxicosis, Branwood (1949) stated that clubbing of the fingers is not seen in this condition I have been unable to find any reference or case-report similar to case 2 (see below) describing the clinical triad of gross digital clubbing, exophthalmic ophthalmoplegia, and untreated active thyrotoxicosis

Case 2.—A warehouseman, aged 54, was admitted to the Bristol Eye Hospital in October, 1956, with six months' history of nervousness, irritability, palpitations, and increasing prominence of his eyes In spite of having a good appetite he had lost almost 2 stones in weight. During the previous four weeks he had had puffy eyelids Pain in his eyes and photophobia had been present for three days

On examination he was nervous and agitated His skin was warm and moist, and a fine tremor of his fingers was present His resting pulse-rate was 130, with normal rhythm His blood-pressure was 180/95 mm Hg His thyroid gland was easily palpable and uniformly enlarged A loud systolic bruit was audible over his neck Bilateral proptosis (exophthalmo-

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* Since there appears to be a wide range of measurements made with a Hertel exophthalmometer in healthy people, the degree of exophthalmos is not given For example, Brain and Turnbull (1938) state that the average normal reading is 12 5 mm , whereas Rundle and Wilson (1945) report the average values in controls measured by the same instrument as 16 9±1 8 mm , with the upper limit of normal as high as 23 0 mm

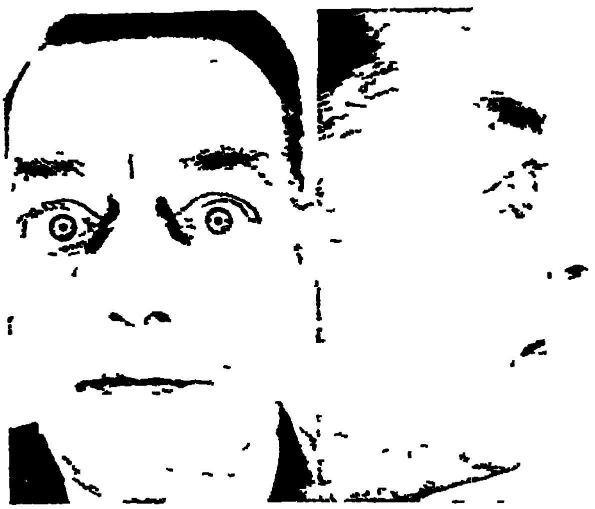

Fig 3—Case 2 malignant exophthalmos.

meter right eye 25 mm., left eye 26 mm.*) was present. Lid lag, lid retraction, and widening of the palpebral fissures were evident. His upper and lower eyelids were œdematous and inflamed, and chemosis was present (fig. 3). There was some weakness of elevation and abduction in both eyes, and the patient complained of double vision when attempting to look to the extreme left and right. His visual acuity was right 6/6, left 6/5, his ocular fundi and visual fields were normal. He had no pretibial myxœdema. He also had gross clubbing of his fingers and toes (fig. 4). He had no enlargement of his hands and feet and no pain or swelling of his ankles, feet, or wrists. His face showed no sign of acromegaly. He had some thickening and furrowing of his skin over his forehead. His heart, lungs, and abdomen were normal clinically.

Investigations.—Complete blood-counts, liver-function tests, and radiography of his thoracic inlet, chest, long bones, hands, and feet were all normal. Radiography of his skull showed no intracranial abnormality, and his sella turcica was normal. Radioactive-iodine measurements showed that the total uptake was 82% of the dose, at four hours, and at 48 hours the protein-bound ^{131}I level in the plasma was 1·35±0·08% of the dose per litre, values consistent with thyrotoxicosis.

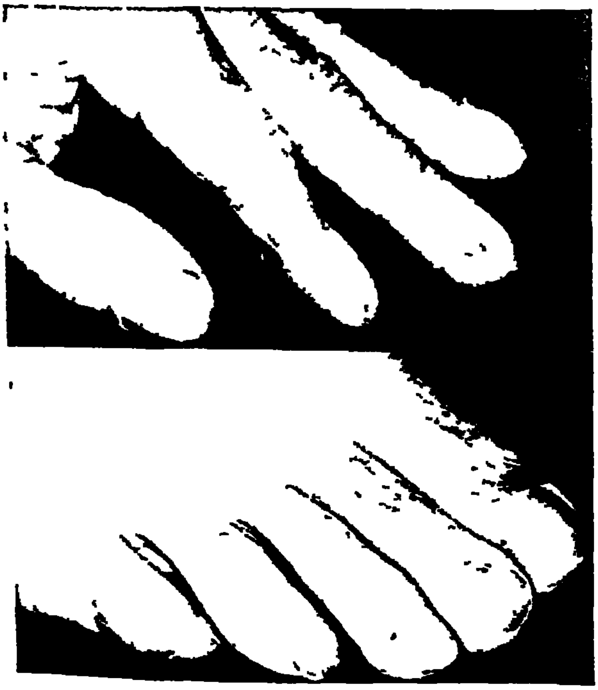

Fig 4—Case 2 clubbing of fingers and toes.

Progress.—Bilateral lateral tarsorrhaphies were done and the patient was transferred to the Bristol General Hospital for radioactive-iodine therapy. He became euthyroid and in twelve months there was definite improvement in his exophthalmos and ophthalmoplegia. His extreme digital clubbing has remained unchanged, and no signs of circumscribed myxœdema have appeared.

Comment.—In this patient there was no family history of digital clubbing and no evidence of cardiac, pulmonary, hepatic, or intestinal disease. Although the skin over his forehead appeared a little thickened and furrowed, he had no prominent skin folds on his cheeks, exaggeration of the normal nasolabial folds, or enlargement of his extremities, all of which are such characteristic features of pachydermoperiostosis (idiopathic osteoarthropathy) (Angel 1957). The patient had first noticed curving of his finger-nails about two or three months before he was seen at the Bristol Eye Hospital.

It therefore appears that the development of digital clubbing closely followed the onset of symptoms and signs of a toxic goitre and progressive exophthalmos. When the patient was first seen in October, 1956—six months after the onset of his thyrotoxic symptoms—gross digital clubbing, exophthalmic ophthalmoplegia, and signs of active thyrotoxicosis were present.

Discussion

Pretibial myxœdema—first described by a Bristol physician (Watson-Williams 1895)—and its association with exophthalmic ophthalmoplegia are now well recognised. The complete clinical triad with gross digital clubbing is evidently rare but apparently not so rare as the paucity of published reports suggests.

Analysis of the published case-reports shows that a definite association between the onset of acropachy, exophthalmic ophthalmoplegia, pretibial myxœdema, and hypothyroidism existed in 2 men (Rynearson and Sacasa 1941, Greene 1951) and 1 woman (Inch and Rolland 1953). In a further 3 cases reviewed the association between acropachy and exophthalmic ophthalmoplegia is not proved, because insufficient data about the time of onset of digital clubbing and the presence of malignant (as opposed to benign) exophthalmos is recorded. Levitt (1953) wrote that he had seen 8 such patients, but he gave no further clinical details.

In the present case 1 the development of severe digital clubbing and progressive exophthalmos with ophthalmoplegia closely followed the onset of classical symptoms and signs of myxœdema. In case 2 gross clubbing of the fingers and toes and exophthalmic ophthalmoplegia developed in a patient with a toxic goitre. No other case of severe digital clubbing in untreated active thyrotoxicosis seems to have been published. There were no signs of pretibial myxœdema in either of these 2 cases.

Clinical Manifestations of Pituitary Dysfunction

Exophthalmic ophthalmoplegia.—The concept expressed by many workers that exophthalmic ophthalmoplegia is due to overproduction of the thyroid-stimulating hormone (T.S.H.) of the anterior lobe of the pituitary gland has been challenged by Gilliland and Strudwick (1956). Using a new method of clinical assay of T.S.H. in the serum which would not be affected by the presence of excess thyroid hormone, these workers found a high level of T S H in most patients with spontaneous myxœdema and in cretins comparable with the raised level also obtained in 8 patients with thyrotoxicosis and severe eye signs Further, the T S H levels in 3 patients with exophthalmic ophthalmoplegia without thyrotoxicosis did not differ from those found in healthy controls Gilliland and Strudwick therefore conclude that oversecretion of T S H *is not the sole cause of exophthalmos*

The supposed existence of an "exophthalmos-producing" hormone, possibly also of pituitary origin, as a separate entity from T S H is supported by the findings of Querido and Lameyer (1956) In 18 thyrotoxic patients *there was no significant difference between the levels of* T S H in the serum of 9 patients without serious eye signs and in that of 7 with serious eye signs Further, the circulating T S H levels were repeatedly low in 1 euthyroid patient who developed malignant exophthalmos after partial thyroidectomy, and were very high in another with only slight proptosis, pretibial myxœdema, and postoperative hypothyroidism Thus there appears to be no direct correlation between the levels of T S H *in the serum and the presence and degree of* exophthalmos

Digital clubbing —The question now to be considered is whether acropachy can ever be regarded as a clinical manifestation of pituitary dysfunction

Bloom (1948) reported chronic hypertrophic pulmonary osteoarthropathy and gynæcomastia *in a man* with a carcinoma of the bronchus He found metastases in the anterior lobe of the pituitary gland at necropsy and suggested that these had excited the production of anterior-lobe hormones in sufficient quantity to produce the bone changes, digital clubbing, and gynæcomastia which had developed during the course of the disease The regression of digital clubbing which often occurs after lung resection clearly excludes stimulation of the hypophysis as a common cause, and Flavell (1956) has shown that severing the vagus nerve on the same side as the affected lung also completely reverses the signs of osteoarthropathy

On the other hand, Fried (1943) has presented evidence in support of dyspituitarism as an ætiological factor in some cases He described the *development of* chronic hypertrophic pulmonary osteoarthropathy, clubbing of the fingers, and clinical and radiological features of acromegaly in 4 patients with a bronchogenic carcinoma Ellman (1953) and Järvinen and Kumlin (1954) also reported similar clinical findings in 4 patients with the same neoplastic condition Hyperplasia of the eosinophil cells of the anterior lobe of the pituitary gland without any metastatic involvement of the endocrine glands was *found in* all 4 patients on whom postmortem examinations were performed

Levitt (1954) wrote

> "The presence of pulmonary osteo-arthropathy in a patient with severe malignant exophthalmos and localised œdema of the legs support the view that the pituitary gland is closely associated with this phenomenon The associated eosinophil hyperplasia present in the pituitary gland adds further support to the view that the growth factor is very closely allied to the proliferative thyroid hormone"

The hitherto unpublished necropsy findings in the case presented by Greene (1951) merit particular emphasis This male patient, with hypothyroidism, gross digital clubbing, malignant exophthalmos, and pretibial myxœdema, died at the age of 76 Some seventeen years before he was first seen by Dr Greene he had been treated with potassium iodine for an apparently non-toxic goitre, and after this treatment the thyroid enlargement had disappeared Necropsy showed severe thickening of the fingers and toes and formation of new bone along the shafts of the metacarpals Pulmonary congestion was present, but there were no signs of a bronchogenic carcinoma *Massive* fibrosis of the thyroid gland and an eosinophil *chromophil* adenoma of the anterior lobe of the pituitary gland were also found

Conclusions

The role of the pituitary gland in the production of exophthalmic ophthalmoplegia and in the *pathogenesis* of digital clubbing has been studied and reviewed by many workers

The concept of an "exophthalmos-producing" hormone as a separate entity from the thyroid-stimulating hormone of the pituitary gland is now widely held In the light of clinical and necropsy findings the development of acropachy and chronic hypertrophic pulmonary osteoarthropathy in some patients with a bronchogenic carcinoma has been ascribed to a disturbance *of* pituitary function In this connection the necropsy findings are of *particular* interest *in* 2 patients with either *medically* induced or postoperative hypothyroidism associated with malignant exophthalmos, pretibial myxœdema, and gross digital clubbing one patient had an *eosinophil chromophil* adenoma of the pituitary gland, the other had eosinophil hyperplasia of the anterior lobe of the pituitary gland

The association of acropachy and exophthalmic ophthalmoplegia in patients with either postoperative or medically induced myxœdema *is not so rare as might be expected* from the paucity of published reports On the other hand, the development of severe digital clubbing and exophthalmic ophthalmoplegia in untreated active thyrotoxicosis (case 2) does not appear to have been previously described

The fact that gross digital clubbing is now reported in association with exophthalmic ophthalmoplegia in hyperthyroid, as well as in induced euthyroid and hypothyroid states, adds further support to the view that this syndrome, with or without pretibial myxœdema, is a clinical manifestation of pituitary dysfunction

I am indebted to Mr C A Brown and Dr A M G Campbell *for permission to publish the two case-reports*, Dr J L James for helpful criticism and advice, and Mr F A Godman, of the department of photography, University of Bristol, for the photographs

REFERENCES

Angel, J H (1957) *Brit med J* ii, 789
Bloom, W (1948) *Ann intern Med* 29, 361
Brain, W R, *Turnbull, H M* (1938) *Quart J Med* 7, 293
Branwood, A W (1949) *Edinb med J* 56, 105
Cushing, E H (1937) *Int Clin* 2, 200
Ellman, P (1953) *Proc R Soc Med* 46, 851
Flavell, G (1956) *Lancet*, i, 260
Fried, B M (1943) *Arch intern Med* 72, 565
Gilliland, I C, Strudwick, J I (1956) *Brit med J* i, 378
Greene, R (1951) *Proc R Soc Med* 44 159
Inch, R S M D, Rolland, C F (1953) *Lancet*, ii, 1239
Järvinen, K A J, Kumlin, T (1954) *Ann rheum Dis* 13, 52
Lancet (1955) i, 340
Levitt, T (1953) *ibid* ii, 1359
— (1954) The Thyroid p 325 Edinburgh
Querido, A, Lameyer, L D F (1956) *Proc R Soc Med* 49, 209
Rundle, F F, Wilson, C W (1945) *Clin Sci* 5, 31
Rynearson, E H, Sacasa, C F (1941) *Proc Mayo Clin* 16, 353
Thomas, H M, *Jr* (1933) *Arch intern Med* 51, 571
Watson-Williams, P (1895) *Clin J* 7, 93

INTRINSIC-FACTOR-INHIBITING SUBSTANCE IN SERUM OF ORALLY TREATED PATIENTS WITH PERNICIOUS ANÆMIA

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PERNICIOUS anæmia has been extensively treated with intrinsic factor for more than twenty-five years, especially in the Scandinavian countries Formerly the preparations consisted of more or less crude dried hog gastric pylorus, but in the past five or six years a new type of oral preparation has become very popular purified hog pyloric mucosa plus vitamin B_{12} It has been shown that only 100 mg of hog pyloric mucosa causes substantial absorption of vitamin B_{12} in pernicious anæmia, and such preparations administered initially almost always produce complete remission. But in prolonged treatment with preparations of this type a considerable proportion of the patients relapse, and several have shown myelopathy—even without hæmatological relapse in the peripheral blood. (Blackburn et al. 1955, Meulengracht 1955, Norregaard 1955, Bastrup-Madsen 1957)

TABLE I—URINARY EXCRETION IN SCHILLING TEST PERFORMED WITHOUT INTRINSIC FACTOR, WITH HOG INTRINSIC FACTOR ALONE, AND WITH HOG INTRINSIC FACTOR MIXED WITH 50 ML. SERUM FROM HEALTHY PERSONS FIGURES ARE PERCENTAGES OF ADMINISTERED ^{60}CO VITAMIN B_{12} EXCRETED IN URINE IN 24 HOURS

Intrinsic factor		
None	100 mg hog pyloric mucosa	100 mg hog pyloric mucosa—50 ml. serum
0·7	15·7	16·3
0·7	15·7	17·0
0·7	15·7	10·4
0	26·6	21·6
0	19·1	27·5
2·2	12·2	8·8
0	21·2	32·0
2·6	18·0	16·1
7·1	28·2	15·3
7·1	28·2	21·0
0	16·4	10·8
0	14·0	18·7
0·7	20·7	16·8
0	16·4	16·5

The cause of the failure of these newer oral preparations is a block in the intestinal absorption of vitamin B_{12} with hog pyloric mucosa as intrinsic factor, the block is not present when homologous intrinsic factor is administered (Schwartz et al 1957) This intestinal block has been confirmed by several workers (Berlin et al 1957, Killander 1957, Lowenstein et al. 1957, Allgen and Tomenius 1958, Stokes and Pitney 1958) but its cause has not been found so far The block may be due to some sort of sensitisation, two groups found no evidence of immunity in such patients, but they did not state how their investigation was carried out. (Stokes and Pitney 1958, Adams 1958) Recently an antibody to Castle's intrinsic factor was reported by Taylor and Morton (1958) They immunised rabbits with intrinsic-factor preparations from man and from pig pylorus and found in the serum of the treated rabbits a substance inhibiting human and pig intrinsic factor respectively

As part of investigations in this hospital into the cause of the intestinal block in orally treated patients with pernicious anæmia several sera from healthy persons and patients with pernicious anæmia were examined for antibody against intrinsic factor

Methods

The Schilling (urinary excretion) test was used throughout, 0·5 μg ^{60}Co vitamin B_{12} (with 0·1 μC) was administered by mouth, and 2 hours later 1 mg unlabelled vitamin B_{12} intramuscularly ^{60}Co vitamin B_{12} excretion was determined in 24-hour specimens of urine.

The patients all had typical pernicious anæmia with a low (0–7·1%) ^{60}Co vitamin B_{12} excretion when tested without intrinsic factor, and a normal ^{60}Co vitamin B_{12} excretion (in this series 12·2–28·2%) with 100 mg hog pyloric mucosa.

TABLE II—URINARY EXCRETION IN SCHILLING TEST PERFORMED WITHOUT INTRINSIC FACTOR, WITH HOG INTRINSIC FACTOR ALONE, AND WITH HOG INTRINSIC FACTOR MIXED WITH 50 ML. SERUM FROM PATIENTS WITH UNTREATED PERNICIOUS ANÆMIA. FIGURES ARE PERCENTAGES OF ADMINISTERED ^{60}CO VITAMIN B_{12} EXCRETED IN URINE IN 24 HOURS

Intrinsic factor		
None	100 mg hog pyloric mucosa	100 mg hog pyloric mucosa—50 ml. serum
0·7	20·7	18·2
0	21·2	15·6
0	16·0	14·9
0	16·4	13·8
0	14·0	15·1
0	16·4	17·7

Serum from healthy persons and four groups of patients with pernicious anæmia was investigated (1) untreated pernicious anæmia, (2) pernicious anæmia treated for 1–5 years with oral preparations of vitamin B_{12} plus hog pyloric mucosa, (3) pernicious anæmia treated orally with a crude stomach preparation ('Pyloron-Exopyloron'), (4) pernicious anæmia treated by injection. 50 ml of serum was used in all experiments

The test for antibody against intrinsic factor was carried out as follows 100 mg hog pyloric mucosa was mixed with a small amount of water and then with 50 ml. serum at room temperature. Ten minutes later the mixture was given with the test dose of ^{60}Co vitamin B_{12}

Results

The results are shown in tables I–IV.

Serum from healthy persons (table I) and patients with untreated pernicious anæmia (table II) does not contain any intrinsic-factor-inhibiting substance

Sera from 21 patients with pernicious anæmia treated orally for more than a year with preparations of vitamin

TABLE III—URINARY EXCRETION IN SCHILLING TEST PERFORMED WITHOUT INTRINSIC FACTOR, WITH HOG INTRINSIC FACTOR ALONE, AND WITH HOG INTRINSIC FACTOR MIXED WITH 50 ML. SERUM FROM PATIENTS WITH PERNICIOUS ANÆMIA TREATED ORALLY WITH PREPARATIONS OF VITAMIN B_{12} PLUS HOG PYLORIC MUCOSA (BENDOGEN, CYCOPLEX) FIGURES ARE PERCENTAGES OF ADMINISTERED ^{60}CO VITAMIN B_{12} EXCRETED IN URINE IN 24 HOURS

Intrinsic factor		
None	100 mg hog pyloric mucosa	100 mg hog pyloric mucosa—50 ml. serum
0·7	15·7	0·3
0·7	15·7	1·0
4·4	15·3	1·4
0·7	20·7	1·4
0·7	15·7	1·6
2·6	18·0	3·7
0·7	15·7	4·2
2·2	12·2	4·3
0	16·4	4·6
0	26·6	5·4
2·6	18·0	7·5
0·7	15·7	7·6
6·9	19·8	7·9
7·1	28·2	8·1
7·1	28·2	8·3
0·7	15·7	11·5
0	25·6	11·8
0	14·0	12·3
0	16·4	15·9
0	16·4	17·0
0	21·2	22·6

TABLE IV—URINARY EXCRETION IN SCHILLING TEST PERFORMED WITHOUT INTRINSIC FACTOR, WITH HOG INTRINSIC FACTOR ALONE, AND WITH HOG INTRINSIC FACTOR MIXED WITH 50 ML SERUM FROM PATIENTS WITH PERNICIOUS ANÆMIA TREATED ORALLY WITH A CRUDE STOMACH PREPARATION FIGURES ARE PERCENTAGES OF ADMINISTERED ^{60}CO VITAMIN B_{12} EXCRETED IN URINE IN 24 HOURS

Intrinsic factor		
None	100 mg hog pyloric mucosa	100 mg hog pyloric mucosa+50 ml serum
0 5	15 7	1 4
0	14 0	1 4
0	14 0	2 2
0	16 4	12·9
0	20 7	10 6
0	14 0	18 4

B_{12} plus hog pyloric mucosa were investigated (table III) 16 of these sera inhibited the intrinsic-factor activity—in several cases almost completely 13 of these 16 patients were investigated with ^{60}Co vitamin B_{12} and 100 mg hog pyloric mucosa, and all were found to have a blocked intestinal absorption, 3 were not investigated, but in at least 1 of these patients absorption was probably blocked (serum-vitamin-B_{12} 32 µµg per ml after two years' treatment)

Of the 5 patients without intrinsic factor antibody in their serum, 3 were investigated, in 2 blockade was found, and the 3rd had normal vitamin-B_{12} absorption

Serum from 6 patients with pernicious anæmia, treated orally for some time (six months to twenty years) with crude stomach preparations, showed gross inhibitory activity in 3 cases (table IV) The intestinal absorption was investigated in all 6 patients, 1 had a slightly reduced absorption (8 7% excretion with the Schilling test), whereas in the other 5 the absorption was normal

Serum from 2 patients treated by injection showed no intrinsic-factor-inhibiting activity

In some cases the experiments were repeated with the same sera ^{60}Co vitamin B_{12} and hog pyloric mucosa were mixed 10 minutes before the addition of serum The intrinsic-factor-inhibiting activity was found unaltered by this procedure (probably indicating that it is directed against the vitamin B_{12} plus intrinsic factor)

3 sera known to inhibit hog pyloric mucosa activity were tested in the same way, using human fundus mucosa as intrinsic factor In 2 cases there was pronounced inhibiting activity against this homologous intrinsic factor

Discussion

Intrinsic-factor-inhibiting activity in sera from patients with pernicious anæmia treated orally has not previously been reported In order to examine as many sera as possible it was decided not to change the procedure in this investigation Further studies, especially serological, are necessary Possibly this intrinsic-factor-inhibiting substance is analogous with the intrinsic-factor-antibody produced experimentally in rabbits by Taylor and Morton (1958)

It is reasonable to assume that it is produced by the oral treatment, and it may partly explain why so many patients with pernicious anæmia, treated orally with vitamin B_{12} plus hog pyloric mucosa, develop a more or less blocked intestinal absorption of vitamin B_{12} But this intrinsic-factor-inhibiting activity cannot alone explain the intestinal blockade Patients treated with crude pig stomach preparations can have a quite normal intestinal vitamin-B_{12} absorption with hog pyloric mucosa and considerable intrinsic-factor-inhibiting activity in their serum Furthermore the inhibiting activity was found to operate against human intrinsic factor

Summary

Intrinsic-factor-inhibiting activity was found in a considerable proportion of sera from patients with pernicious anæmia treated orally Serum from healthy persons and patients with untreated pernicious anæmia contained no such activity

As intestinal absorption of vitamin B_{12} proved to be normal in some cases with inhibiting activity in the serum, and as the intrinsic-factor-inhibiting activity was shown to operate also against human intrinsic factor, such activity is probably not the sole cause of the intestinal blockade following long-continued oral treatment of pernicious anæmia

I wish to thank Medicinalco, Ltd , of Copenhagen, for liberal supplies of intrinsic factor This study was supported by the Statens Videnskabsfond, University of Copenhagen

REFERENCES

Adams, J F (1958) *Brit med J* i, 644
Allgén, L -G , Tomenius, J (1958) *Svenska Läkartidn*, 55, 437
Bastrup-Madsen, P (1957) *Nord Med* 34, 1233
Berlin, R , Berlin, H , Brante, G (1957) Congress of the European Society of Hæmatology, abstract, 227
Blackburn, E K , Cohen, H , Wilson, G M (1955) *Brit med J* ii, 461
Killander, A (1957) *Lancet*, i, 1041
Lowenstein, L , Brunton, L , Shapiro, L , De Leeuw, N , Dufresne, M (1957) *Canad med Ass J* 77, 923
Meulengracht, E (1955) *Ugeskr Læg* 117, 883
Nørregaard, S (1955) *ibid* p 850
Schwartz, M , Lous, P , Meulengracht, E (1957) *Lancet*, i, 751
Stokes, J B , Pitney, W R (1958) *Brit med J* i, 322
Taylor, K B , Morton, J A (1958) *Lancet*, i, 29

FACIAL SINUSES SECONDARY TO PULMONARY TUBERCULOSIS

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IN three cases referred to us for the treatment of discharging sinuses on the face the lesions were found to be secondary to pulmonary tuberculosis We know of only one such case (Oppenheim et al 1950) previously reported

Case-reports

Case 1—A man, aged 33, had had an "abscess" in the left upper premolar region, 8 months previously This was incised externally, but continued to discharge through a sinus He had recently noted dyspnœa and a cough

On the left cheek, about 1½ in distal to the angle of the mouth, was a depressed scar surrounding a sinus from which watery straw-coloured pus was discharging Below the outer canthus of the left eye was a healed sinus with surrounding scar tissue, the centre of which was fluctuant (fig 1) The dental condition was poor A thick fibrous band was palpable in the buccal sulcus running from the alveolus in the $\underline{|45}$ region to the cheek Roots of the $\underline{|45}$ teeth were present,

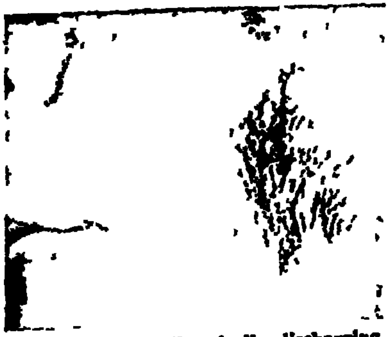

Fig 1—Case 1 Chronically discharging facial sinus

and radiographs showed rarefaction round the apices. *Staphylococcus albus* and *aureus*, sensitive to penicillin, were cultured from pus from the sinus, no actinomyces were seen. Intramuscular penicillin was given. All his teeth were removed, under a general anaesthetic, and the sinus on the cheek was explored. It appeared to end in the alveolar bone in the /45 region. No healing of the sinus took place, and cultures a week later produced *Staph albus*, sensitive only to chloramphenicol. This antibiotic was now given in place of penicillin.

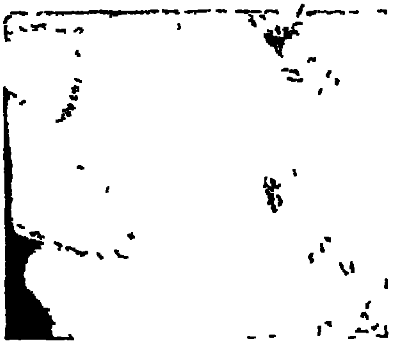

Fig 2—Case 1 Sinuses healed after systemic treatment for pulmonary tuberculosis

The temperature charts showed a "swinging" pattern like that seen in a tuberculous infection. Radiographs of the chest showed effusion at the base of both lungs and granular mottling throughout both lung fields, with some cavitation at the apices, suggestive of pulmonary tuberculosis. The sputum contained acid- and alcohol-fast bacilli, and pus from the sinus yielded tubercle bacilli, in pure culture.

When the patient was seen 12 months later, after medical treatment, the sinuses had healed and the scarring was much reduced (fig 2).

Case 2.—A man, aged 22, was referred for a submandibular swelling. 4 weeks previously, the tooth had been extracted because of an acute alveolar abscess. The submandibular swelling had then increased in size, and his doctor had incised and drained it, since when it had been discharging.

Midway along the left mandible and below its lower border was a fluctuant area, about 2 cm in diameter, surrounded by an area of fibrous tissue. The overlying skin was hyperæmic, and there were signs of a partially healed sinus. There was a second smaller swelling below the main area, and slight left submandibular adenitis. No intra-oral abnormalities were noted, the /7 socket was healing normally.

The sinus in the left submandibular region was reopened, and produced watery straw-coloured pus. Radiographs of the left mandible showed no lesion. Cultures of the discharge grew coagulase-negative staphylococci sensitive to penicillin.

Penicillin was given, but after a week there was little change in the condition. Accordingly, under general anæsthesia the sinus and the surrounding scar tissue was excised. A mass of granulation tissue was found with finger-like extensions, this was removed and the wound closed in layers. 14 days after operation a watery yellow discharge was coming from the two suture holes. At this stage tuberculosis was diagnosed in case 1, and in view of the similarity of his lesions, the second patient was also referred for a chest radiograph, which revealed a tuberculous appearance in the left lung. With appropriate medical treatment, the sinuses rapidly healed.

Fig 3—Case 3 Chronically discharging sinus in the left submental region

Case 3.—A man, aged 33, had a fracture of the right mandible involving an unerupted premolar tooth. Splints were applied by means of peralveolar and circumferential wires, fixation was achieved and maintained for 6 weeks, and union took place.

5 months later he returned with a discharging sinus in the left submental region (fig 3). It had begun a week earlier as a painless swelling, which had increased in size, burst, and drained extraorally, with persistent discharge.

A swelling about $^3/_4$ in. in diameter was present in the left submental region. Pressure produced watery pus. The sinus coincided with the puncture hole that had been made in the skin to pass the circumferential wire. No intra-oral abnormalities were noted, and radiographs of the left mandible revealed no lesion.

Again the striking similarity of the lesion to that in case 1 prompted us to order an immediate chest radiograph, and this showed infiltration of the right and left upper and mid zones of the lungs. Bilateral cavitation was evident, and the sputum contained acid- and alcohol-fast bacilli. With treatment of his pulmonary tuberculosis, the submental lesion healed, and after 17 weeks there was only a scar (fig 4).

Discussion

Tuberculous ulceration of the mouth may be primary or secondary. Secondary infection is more common, Cameron (1939) quoted an incidence of 1 case of ulceration in 1892 cases of pulmonary tuberculosis. The small numbers of cases suggest that the tissues of the oral cavity offer resistance to tuberculous infection. The explanation of this might be (1) resistance of epithelium to the invading organisms, (2) protective and germicidal action of saliva (3) rich blood-supply of the region, (4) constant movements of the tongue and cheeks, preventing long contact with the bacilli, or (5) antagonistic action of various bacteria to one another.

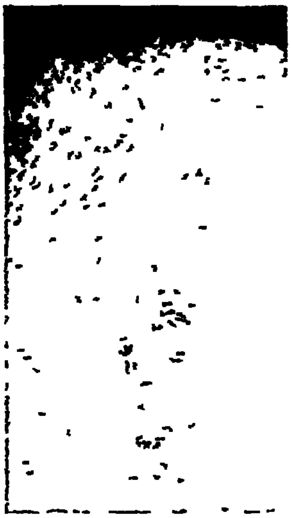

Fig 4—Case 3 Sinus healed after systemic treatment for pulmonary tuberculosis

Chapotel (1930) wrote that only 50 cases of tuberculosis of the mandible had been reported up to 1922, and it was always associated with tuberculosis elsewhere. He suggested the following pathways by which infection reached the jaws (1) from a tuberculous lesion of the gingivæ, (2) from infected sputum through the gingival tissues during tooth eruption, and (3) hæmatogenous spread.

Port and Euler (1951) thought that spread of tubercle bacilli to the jaw is more likely to be hæmatogenous than via a carious tooth, they cited the incidence of tuberculous infection of the zygomatic process, despite its relative great distance from the teeth.

Meng (1940) described 14 mandibular bone lesions, in 10 of which the chest was studied radiographically and revealed pulmonary tuberculosis.

60% of Chapotel's patients were under the age of 15, whereas Meng's patients varied in age from 4 to 48, 11 being between 10 and 30. Pilcher and Trauner's (1948) findings were similar to Chapotel's.

Partsch (1904), Darlington and Salman (1937), Gomouec (1939), and Brodsky (1942) demonstrated tubercle bacilli in the periapical tissues of a tooth Infection of sockets following extractions has occurred in patients with pulmonary tuberculosis (Burman and Jonsson 1935)

Oppenheim et al (1950) reported one case of pulmonary tuberculosis where a fistula arose from the buccal mucosa through the skin of the cheek

There is a similarity in our three cases The first two patients complained of a " dental abscess ", and the third a swelling similar to a dental infection, as the initial symptom None had pain The discharging sinuses had the chronicity and lack of inflammatory symptoms of a tuberculous " cold abscess ". The sinuses and discharge were strikingly similar, together with an abnormal amount of fibrous tissue, especially in the first two cases

It can be assumed that the lesions of the jaws were secondary to those in the lungs, but the route of infection is debatable In cases 1 and 2 retained roots and carious teeth were present, allowing ingress of bacilli In case 1 the tubercle bacilli in the sputum could have entered via the retained roots or through the blood-stream, and secondarily infecting a non-specific granuloma In case 2 infection could have followed the extraction, if it was not already present In case 3, we think, tubercle bacilli from the sputum tracked down the circumferential wire to the soft tissues From the removal of the wire 5 months elapsed before the lesion appeared in the left submental region

In our cases infection spread by the sputum seems more likely than infection via the blood The staphylococci in the discharge, presumably arising from infected teeth, initiated an abscess and a sinus which favoured the superimposition of tuberculous infection

Three constant factors in our cases are

They had active pulmonary tuberculosis

Pathways from mucous membrane to skin existed and opened up a route of infection by sputum

A typical and easily recognisable facial lesion developed

The clinical picture suggests that the deeper dermal layers have relatively little resistance to tuberculous infection, for mucous membrane, bone, periosteum, overlying soft tissues and skin were subjected to the same infection but were unaffected Except the dermal structures, all healed normally

Summary and Conclusion

Three cases are reported in which investigation of sinuses associated with jaws led to the diagnosis of unsuspected pulmonary tuberculosis

In the treatment of dental conditions care should be taken to prevent external sinus formation, and to maintain a healthy mouth during treatment, even if this necessitates extensive conservative treatment of the teeth and gums

We are indebted to Dr Henry B Slater, chest physician of Ashton-under-Lyne, for advice and progress reports on cases 1 and 3 We also thank Miss J L Perry, of Crumpsall Hospital, Manchester, for the photographs

REFERENCES

Brodsky, R H (1942) *Amer J Orthodont* 28, 132
Burman, B , Jonsson, F (1935) *Sverig Tandlak Forb Tidn* 28, 343
Cameron, C (1939) *Brit J Tuberc* 33, 157
Chapotel (1930) *Rev odont* 51, 444
Darlington, C G , Salman, I (1937) *Amer Rev Tuberc* 35, 147
Gornouec, L (1939) *Rev Stomat , Paris* 41, 164
Meng, C M (1940) *J Bone Jt Surg* 22, 17
Oppenheim H , Livingston C S , Mixon, J W , Miller, C D (1950) *Arch Otolaryng , Chicago*, 6, 910
Partsch, C (1904) *Dtsch Zahnheilk Vortr*
Pilcher, H , Trauner, R (1948) Mund- und Kiefer-Chirurgie, vol II, p 137 Vienna
Port, G , Euler, H (1951) in Hofer, O Lehrbuch der Klinischer Zahnheilkunde, pp 416–418, 450–452 Munich

ANTIBIOTIC-RESISTANT STAPHYLOCOCCAL OUTBREAKS IN A MEDICAL AND A SURGICAL WARD

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OUTBREAKS of staphylococcal infection in hospital wards are now common The two reported here are of special interest because in both cases the origin was traced to an infected patient admitted to the ward, and the strains isolated were resistant to erythromycin as well as to penicillin, streptomycin, and tetracycline

The first outbreak was in a male medical ward Although the epidemic strain was scattered through the ward it was responsible for no severe infection and was eliminated without closure of the ward

The second outbreak, which was in a male surgical ward, was responsible for 11 infections, many of which were severe, and was controlled only by closing and disinfecting the ward

Bacteriological Methods

Staphylococci from infections were isolated in the routine laboratory on blood-agar plates, and all coagulase-positive strains were kept for further investigation Nutrient-agar plates containing phenolphthalein phosphate (Barber and Kuper 1951) were used for isolating staphylococci from nasal swabs, bedding, curtains, and the air of the wards Phosphatase-positive colonies were tested for the production of coagulase, and coagulase-positive strains were kept for further investigation Samples from bedding were taken by the sweep-plate technique of Blowers and Wallace (1955)

All coagulase-positive strains isolated in this way were tested for sensitivity to penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, and novobiocin by the ditch-plate method The concentrations of antibiotics used in the ditch were for penicillin 10 units per ml , streptomycin 50 or 200 µg per ml , chloramphenicol 50 µg per ml , and tetracycline, erythromycin, and novobiocin 25 µg per ml The Oxford staphylococcus was streaked across each plate as a control Strains were recorded as sensitive if they showed a degree of sensitivity similar to that of the Oxford staphylococcus, resistant if they grew up to or across the ditch, and partially resistant if there was an intermediate degree of inhibition

Representative strains were phage-typed by the method of Williams and Rippon (1952) using 21 phages

Outbreak in Medical Ward

This ward was first studied in November, 1957, as part of an investigation into the incidence of strains of *Staphylococcus pyogenes* in the hospital environment Nasal swabs were taken from all the patients and staff, and sweep-plates were made from the bottom and one top blanket of each patient and from one curtain round each bed

Antibiotic Sensitivity of Strains Isolated

The number of strains of *Staph pyogenes* isolated and their sensitivity to antibiotics are given in table I, which shows that strains resistant to penicillin, streptomycin, tetracycline, and erythromycin were isolated from eight blankets, three curtains, and the nasal swabs of 3 patients The bedding of 7 patients was involved, 4 of whom were not apparently harbouring this type of staphylococcus in their anterior nares Where strains with other patterns

TABLE I—STRAINS OF STAPH PYOGENES ISOLATED FROM MEDICAL WARD

Source	No examined	Total*	Strains of *Staph. pyogenes* isolated: Sensitivity to penicillin, streptomycin, tetracycline, and erythromycin (in that order) SSSS	RSSS	RSRS	RRRS	RRRR
Patients nasal swabs	22	20 (*15*)	3	7	2	5	3
Blankets	46	20 (*17*)		6	1	5	8
Curtains	26	6 (*6*)		2		1	3
Staff nasal swabs	19	12 (*12*)	2	10			

R, resistant. S, sensitive.
* Figures in parentheses show number of specimens yielding *Staph. pyogenes*

of resistance to antibiotics were found in bedding, in most cases this was in association with nasal carriage Strains resistant to more than one antibiotic were not isolated from any of the staff

All the strains were also tested for sensitivity to chloramphenicol and novobiocin. All were sensitive to novobiocin, but 2 of the 14 erythromycin-resistant strains were also resistant to chloramphenicol, and 2 of the other erythromycin-resistant strains yielded chloramphenicol-resistant variants

Phage-typing Results

Of the 14 erythromycin-resistant strains 13 were tested for sensitivity to bacteriophages and showed an identical pattern 53/75/77

Of the strains resistant to penicillin, streptomycin, and tetracycline but sensitive to erythromycin 7 were found to be of five different types, all of group III 21 strains resistant to penicillin only were of ten different types, comprising strains of each of the three main phage-groups

Source and Spread of Epidemic Strain

It seems clear from the foregoing results that a single strain of staphylococcus resistant to penicillin, streptomycin, tetracycline, and erythromycin was spreading round the ward The 7 patients whose bedding was infected were not confined to any one area The blankets of 5 patients, including 2 of the 3 nasal carriers, yielded only a few *Staph pyogenes* The 6th patient (A) had a top blanket heavily contaminated with this organism, but no coagulase-positive staphylococci were isolated from his nose, his bottom blanket, or the curtain surrounding his bed Subsequently he was found to have a facial dermatitis infected with the epidemic strain

In the 7th patient a heavy growth of the organism was isolated from his nose, both blankets, and the curtain round his bed He had eczema of one leg with a generalised infected sensitisation dermatitis, and a heavy growth of the epidemic strain was obtained from skin swabs He had been in the ward six weeks and had been treated with prednisone and corticotrophin together with penicillin and streptomycin and later with tetracycline For the last week he had been up for part of the day and allowed to wander round the ward. It seems almost certain that he was responsible for the dissemination of the erythromycin-resistant staphylococcus There is, however, no evidence that he brought the organism into the ward with him. He had been in the hospital for two months earlier in the year and had attended as an out-patient for many months He had not been treated with erythromycin.

Control

Although no infections had resulted from the dissemination of this staphylococcus, in view of its antibiotic resistant pattern it was considered highly dangerous, and steps were taken to eradicate it. The patient who disseminated the strain was discharged, and the 2 patients carrying the epidemic strain in the nose were treated with neomycin-bacitracin cream All the bedding and curtains were changed, and the clean blankets supplied were treated with a quaternary ammonium compound ('Arquad') The floor was thoroughly washed with cresol

Five days later sweep-plates were again taken from two blankets and one curtain of each bed *Staph pyogenes* was isolated from no curtains and from the blankets of only two beds From one of these, seven colonies of a strain resistant to penicillin, streptomycin, and tetracycline but sensitive to erythromycin were isolated From the other bed the epidemic erythromycin-resistant strain was isolated This bed was that of patient A, whose top blanket had previously yielded a heavy growth of this organism, although it was not isolated from the patient's nose The patient, however, was found to have a mild dermatitis of his face, and swabs from this yielded a similar staphylococcus After his discharge and his bedding had been superseded by arquad-treated blankets the strain disappeared from the ward and in the subsequent two months was never isolated from patients or bedding

Outbreak in Surgical Ward

The staphylococcal outbreak (Oct 26 to Dec. 28, 1957) in the surgical ward was very different from the one just described A single strain of *Staph pyogenes* of phage type 80 caused infections of which many were very severe and one fatal in 11 people, including 2 nurses and 1 surgeon (table II) In all the cases the strain was resistant to penicillin and tetracycline, sensitive or partially resistant to streptomycin, and sensitive to novobiocin The sensitivity to erythromycin varied, this was almost certainly due to the fact that case 1, who initially was infected with an erythromycin-sensitive organism, yielded an erythromycin-resistant variant after treatment with this antibiotic (see below) In case 8 a chloramphenicol-resistant variant was isolated, this finding is unexplained

Fatal Case

Attention was first drawn to the ward because a patient (table II, case 2) had died of a fulminating staphylococcal pneumonia

TABLE II—INFECTIONS IN OUTBREAK IN SURGICAL WARD

Case no	Bed no.	Date of isolation of *Staph pyogenes*	Source	Sensitivity to: Penicillin	Streptomycin	Tetracycline	Chloramphenicol	Erythromycin
1	8	Oct. 28, 1957	Boil	R	S	R	S	S
		Nov 18, ,,	Wound	R	PR	R	S	R
		Dec. 3, ,,	Inguinal abscess	R	PR	R	S	R
2	2	,, 3, ,,	Sputum	R	PR	R	S	R
3	1	,, 9, ,,	Boil	R	PR	R	S	R
4	Nurse	,, 9, ,,	Septic finger	R	PR	R	S	R
5	8	,, 11, ,,	Sputum	R	PR	R	S	R
		,, 12, ,,	Transfusion wound	R	PR	R	S	R
		,, 18, ,,	Amputation wound	R	PR	R	S	R
6	11	,, 18, ,,	Wound	R	PR	R	S	R
7	Nurse	,, 20, ,,	Septic finger	R	PR	R	S	R
8	23	,, 23, ,,	Wound	R	PR	R	R	R
9	Surgeon	,, 31, ,,	Abscess	R	S	R	S	S
10	3–11	,, 31, ,,	Sputum	R	PR	R	S	S
11*	14	Jan 11, 1955	Sputum	R	PR	R	S	R

PR partially resistant R, resistant S, sensitive.
* This patient had been transferred to another ward.

He had been admitted on Nov 21, 1957, with acute intestinal obstruction He was extremely ill from his abdominal condition and also had bronchitis He was treated by aspiration and with intravenous fluids, penicillin, and streptomycin A few days later he was considered fit for operation, volvulus of the cæcum with patchy gangrene was found but no generalised peritonitis His cæcum, his appendix, and part of his ascending colon were excised, and an end-to-end anastomosis was made A course of tetracycline was started

After operation the patient made a remarkable recovery and was up and looking well when, on the eighth postoperative day, he developed acute respiratory symptoms with thick purulent sputum which was choking him Tracheotomy gave temporary relief, but his condition rapidly deteriorated, and he died within forty-eight hours of the onset of respiratory symptoms

Necropsy revealed extensive infection of his lungs, but the condition of his abdomen was satisfactory

Source of Infection

About a month previously, on Oct 26, a patient (table II, case 1) had been admitted to the ward with multiple septic spots and boils due to a strain of *Staph pyogenes* resistant to penicillin and tetracycline, partially resistant to streptomycin, and sensitive to chloramphenicol, erythromycin, and novobiocin He was treated with erythromycin alone 250 mg six-hourly for seven days to clear up his skin sepsis On the fifth day of this treatment a recurrent pilonidal sinus in his sacral region was excised On Nov 18, ten days after operation, his wound showed signs of infection, and pus from it yielded a strain of *Staph pyogenes* resistant to erythromycin, penicillin, and tetracycline, and partially to streptomycin A fortnight later he developed an inguinal abscess from which a similar staphylococcus was isolated

Subsequent investigation showed that the erythromycin-sensitive *Staph pyogenes* isolated from him on admission and the erythromycin-resistant strains isolated from the wound and the inguinal abscess some weeks later were all of the same phage type—type 80 It is therefore clear that the strain had developed resistance as a result of the seven days' treatment with erythromycin Since the strain isolated from the fatal case of pneumonia was of the same phage type, it seemed probable that this patient (case 1) was the source of infection

Staphylococci in Environment

Bedding—Sweep-plates were taken from two blankets and one curtain of each bed on Dec 5 Table III shows that *Staph pyogenes* was isolated from the blankets of 13 patients and the curtains of 12, ten of these twenty-five strains were resistant to penicillin and tetracycline, and nine others to these two antibiotics and erythromycin All the erythromycin-resistant strains, tested by bacteriophage, were type 80, and two of eight strains resistant to penicillin and tetracycline but not to erythromycin were also type 80

Staff carriers—On Dec 11 nasal swabs were taken from 10 nurses, 6 carried *Staph pyogenes*, one of the strains was sensitive to all the antibiotics tested, four were resistant to penicillin alone, and one, from the ward sister, was resistant to penicillin, tetracycline, and erythromycin This last strain was phage type 80 *Staph pyogenes* was isolated from only two nasal swabs of 11 doctors studied, and in both instances the strain was resistant to penicillin alone

Air samples—With a slit-sampler three samples of air were taken from each of four widely separated sites in the ward into nutrient agar containing phenolphthalein phosphate and tetracycline 10 µg per ml The 100 c ft of air thus sampled yielded eleven colonies of *Staph pyogenes* resistant to penicillin and tetracycline Nine of these colonies were resistant to erythromycin, and those tested were all phage type 80

TABLE III—STRAINS ISOLATED FROM BLANKETS AND CURTAINS IN OUTBREAK IN SURGICAL WARD

Date (1957)	—	Total	No of beds with infected blankets and curtains			
			Antibiotic sensitivity of strains isolated			
			S to all tested	R to penicillin only	R to penicillin and tetracycline	R to penicillin, tetracycline, and erythromycin
Dec 5	Blankets	13	2	2	4	5
	Curtains	12	1	1	6	4
ALL BLANKETS AND CURTAINS SUPERSEDED BY ARQUAD-TREATED FABRICS						
Dec 16	Blankets	9	4	3	1	1
	Curtains	2				1
Dec 30	Blankets	4		2	1	1
	Curtains	1		1		

R, resistant S, sensitive

Attempts to Control Infection

Case 1 was transferred to a side-ward, and the ward sister who carried the epidemic strain in her nose was treated with neomycin-bacitracin cream and permitted in the ward only when adequately masked The blankets, counterpanes, and curtains from all the beds were changed on Dec 6 For the blankets were substituted immediately blankets treated with a quaternary ammonium compound (arquad), and the curtains which had been removed were similarly treated and then returned to the ward Ten days later, sweep-plates taken from the blankets and curtains of all the beds gave the results shown in table III, which shows that, although the number yielding *Staph pyogenes* was very much smaller, one blanket and one curtain carried the strain resistant to penicillin, tetracycline, and erythromycin

Table II shows that, during this ten-day period, 2 more patients and 1 nurse developed infections due to strains of the same phage type Case 3, with a boil, had recovered from his operation and was discharged, and the nurse was sent off duty Case 5 had a very severe staphylococcal pneumonia as well as infection of an amputation stump and a transfusion wound He was transferred to a side-ward and treated with vancomycin, to which he made a dramatic response

At this stage attempts were made to spray the floor and the lower part of the walls of the ward with a quaternary ammonium compound, but, when the same strain of staphylococcus had infected the wounds of 2 more patients and the finger of 1 other nurse, it was decided on Dec 28 to close the ward Before the ward was empty, 1 further patient developed a chest infection and 1 surgeon developed an axillary abscess Finally 1 patient who had been transferred to a medical ward with pulmonary tuberculosis was found to be superinfected with the epidemic strain of staphylococcus

Nasal Carrier State of Patients and Staff at Time of Ward Closure

The nasal carrier state of patients and staff at this stage is analysed in table IV, which shows that only 6 of 20 patients carried *Staph pyogenes*, but in 2 the strains were resistant to penicillin, tetracycline, and erythromycin Of 15 nurses studied 12 carried *Staph pyogenes* 10 a strain

TABLE IV—CARRIER STATE OF PATIENTS AND STAFF ON DEC 30, 1957, IN OUTBREAK IN SURGICAL WARD

—	No examined	No carrying *Staph pyogenes*				
		Total	Antibiotic sensitivity of strains isolated			
			S to all tested	R to penicillin only	R to penicillin and tetracycline	R to penicillin, tetracycline, and erythromycin
Patients	20	6	1	3	-	2
Nurses	15	12		10	1	1
Doctors	11	4		2	2	
Domestics, porters, physiotherapy, and X-ray staff	26	9	6	3		

resistant to penicillin alone, 1 to penicillin and tetracycline, and 1 to these two antibiotics and erythromycin This last was not the ward sister but a nurse who, when tested on Dec 11, was carrying a strain sensitive to all the antibiotics tested Of 11 doctors tested 4 carried *Staph pyogenes* 2 of the strains were resistant to penicillin only, and 2 to penicillin and tetracycline The group consisting of domestics, porters, and the staff of special departments, whose contact with patients was slight, is of interest in that most of the strains isolated were sensitive to all the antibiotics tested

Effect of Closure of Ward and Spraying with Cetrimide

Those patients well enough to go home were discharged, 2 patients still infected with the epidemic strain were transferred to a fever hospital, and the 9 remaining patients, after their nose, skin, and bedding had been shown to be free from the infecting staphylococcus, were sent to other wards of the hospital The whole ward, including side-rooms and corridor, was then thoroughly sprayed with cetrimide

Air-dust samples—In the next four days the air of the ward was sampled by exposing petri dishes containing nutrient agar plus phenolphthalein phosphate for two and a half hours Swabs were also taken from the dust on the floor and plated out on a similar medium In the main ward 49 plates were exposed and 24 dust swabs examined Of the 73 plates thus used penicillin 10 units per ml was added to the medium in 23, erythromycin in 26, and no antibiotic in 24 No colonies of *Staph pyogenes* were isolated from any of these plates

Similar tests were made in the side-rooms and the adjoining corridor, these consisted of three side-wards, kitchen, bathroom, sluice, linen-room, office, and laboratory In each room 2–4 plates were exposed and 2 dust swabs were taken, in the corridor 5 plates were exposed and 3 dust swabs taken. In all, 49 plates were used 18 contained penicillin, 19 erythromycin, and 12 no antibiotic No *Staph pyogenes* was isolated from the dust swabs, but 2 of the exposed plates yielded coagulase-positive staphylococci One of these, containing penicillin, had been exposed in the linen-room and yielded two colonies, the other, containing erythromycin, had been exposed in the corridor just outside the linen-room and yielded one colony All three colonies were of the epidemic type

In view of the negative results obtained everywhere except in the linen-room, in spite of the rather searching tests in which large numbers of plates had been exposed for two and a half hours, it was decided to fumigate the linen-room without retreatment of the rest of the ward Twenty-four hours after this had been done, 9 plates without antibiotic were exposed for two and a half hours in the linen-room and the adjoining corridor Four colonies of *Staph pyogenes* were isolated from 1 plate exposed in the corridor Since none of these was resistant to any other antibiotic than penicillin, it was decided to reopen the ward

Bedding—The beds were all made up with linen and blankets treated with arquad, and similarly treated curtains were supplied Sweep-plates were taken from two blankets and one curtain of each bed before the admission of patients *Staph pyogenes* was isolated from one blanket and one curtain In each case only a single colony was found, that from the blanket was sensitive to all the antibiotics tested, and that from the curtain was resistant to penicillin only

Discussion

In each of these outbreaks a single strain of *Staph pyogenes* resistant to penicillin, tetracycline, and erythromycin was widespread in the ward environment, and in each case there is evidence that the strain was introduced into the ward by a patient with superficial skin sepsis Although the epidemic strain was isolated from the sister in the surgical ward, more probably she was a reflection of the epidemic than its cause, since strains of *Staph pyogenes* resistant to erythromycin had not been found in this ward before the admission of case 1 and were very uncommon elsewhere in the hospital None such had been found when nasal swabs from 540 nurses were examined ten weeks previously

The outbreak in the medical ward was associated with no severe sepsis, and the strain was apparently eradicated by removing the infected patient, treating the nasal carriers, and changing all the blankets for those treated with a quaternary ammonium compound In the surgical ward, however, there were 11 cases of infection, many of them severe, and the strain was eliminated only after closure of the ward and spraying with cetrimide

Probably both the host and the parasite played a part in this difference As regards the host, patients after operations are highly susceptible to infection McDermott (1956) has suggested that an " increased congregation of more susceptible hosts " is one of the main reasons for the apparent increase in staphylococcal infections in hospitals today

The virulence of the invading staphylococcus must not, however, be overlooked *Staph pyogenes* of phage type 80, the type responsible for the outbreak in the surgical ward, was first isolated in 1953 by Rountree and Freeman (1955) in Australia They regarded the strain as a new phage type of *Staph pyogenes* of " enhanced virulence ", because of the severity of the lesions and the predominance of this strain in outbreaks of neonatal infection in 1954 throughout Australia Since then other workers have reported outbreaks of unusually severe staphylococcal infection due to strains of this type in Great Britain (Anderson and Williams 1956, Gillespie and Alder 1957, Duthie 1957)

It cannot be assumed from this that strains of certain phage types are necessarily more virulent than those of other types Probably the virulence of most strains of *Staph pyogenes* may become enhanced in infections (Barber and Burston 1955) and by passage through patients (Rountree and Freeman 1955, Beaven and Burry 1956)

Antibiotic Sensitivity of Infecting Strains

In the surgical ward the infecting strain was initially erythromycin-sensitive but yielded an erythromycin-resistant variant during the treatment of 1 patient with this antibiotic for seven days Such occurrences are well known with erythromycin (Wise et al 1955, Thomson et al 1956), and Hobson (1954) and Garrod and Waterworth (1956) have shown that staphylococci produce strains resistant to erythromycin more readily than they produce strains resistant to any other antibiotic except streptomycin

In both wards an occasional variant resistant to chloramphenicol was found This finding is unexplained, and there is no known correlation between resistance to erythromycin and resistance to chloramphenicol Since both the infecting strains were resistant to several antibiotics, it is possible that they were highly mutagenic Chadduck et al (1954), working with *Escherichia coli* K 12, have shown that certain strains of this species have mutator genes, which give them an increased rate of mutation to drug resistance and other characteristics The same may be true of staphylococci

Preventive Measures

As long as septic cases are admitted to general wards, hospital cross-infection will continue The present study shows the importance of superficial skin infections in this respect and confirms the observation of Barber and Bursten (1955) that nasal carriers may be relatively unimportant In both wards numerous strains of *Staph pyogenes* were present in the environment, but a newly introduced strain spread round the ward to a much greater degree than any of the strains previously present It is improbable that all strains of *Staph pyogenes* could be excluded from a ward, but, if we really face the fact that staphylococcal sepsis is a communicable disease, there is nothing to prevent hospitals from having isolation blocks to deal with this problem

Meanwhile something, no doubt, can be done by barrier nursing and by treating the bedding The difficulty of applying the former adequately in a busy general ward is, however, extreme The danger of blankets as a source of infection can be reduced Barnard (1952) showed that they were not only sterilised by impregnation with estyl pyridinium bromide ('Fixanol C') but also remained, to some extent, self-disinfecting Blowers and Wallace (1955) and Frisby (1957) recommended washing the blankets in a non-ionic detergent ('Lissapol') and then soaking with a cationic detergent ('Currasol') In the present study arquad was the quaternary ammonium compound used

Finally the whole hospital policy in relation to staphylococci needs reviewing It would almost certainly be impossible and not necessarily desirable to eliminate the whole genus from the hospital environment It might be more sensible and would certainly be more practicable to select relatively harmless strains There is much evidence that pathogenic and non-pathogenic staphylococci are variants of a single species, and that white, golden, or even lemon-yellow strains may, under certain rare conditions, arise one from another (Hoffstadt and Youmans 1932, Pinner and Voldrich 1932, Barber 1955) Certainly strains of staphylococci may show all permutations or combinations in relation to the production of pigment and of alpha-lysin, coagulase, and other toxic substances (Barber et al 1953)

The haphazard and wholesale use of antibiotics in hospitals in the last fifteen years has selected strains of staphylococci which are not only resistant to many of these powerful weapons but also, possibly because they have been freed from competition with lesser breeds, liable to give rise to strains of enhanced virulence (Howe 1954, Beaven and Burry 1956, Barber 1958) A hospital antibiotic policy designed to reverse this process, in association with the exclusion of multiple-resistant strains from the general wards, might have far-reaching results It may well be that the best approach to the problem of staphylococcal cross-infection is to learn how to select staphylococci of lower infectivity and virulence and to render human beings more resistant to their toxic products In the New Jerusalem, when the lion lies down with the lamb, is it too much to hope that man will have learnt to live at peace with the staphylococcus?

Summary

Staphylococcal outbreaks in a medical ward and a surgical ward are described Each was due to the admission of a patient with superficial staphylococcal infection

In both outbreaks the offending staphylococcus was resistant to erythromycin as well as to penicillin, streptomycin, and tetracycline, and in one outbreak the erythromycin resistance followed treatment of the initial patient with this antibiotic

In the medical ward, although the bedding of 7 patients, in widely scattered areas of the ward, was infected, there were no cases of severe sepsis After the infected patients had been discharged and all the blankets and ward curtains had been superseded by fabrics treated with a quaternary ammonium compound, the epidemic strain was no longer found

In the surgical ward a single strain of *Staph pyogenes* of phage type 80 caused severe infections (of which one was fatal) in 8 patients, 2 nurses, and 1 surgeon The offending strain was only eliminated by closing the ward and by spraying with cetrimide

It is a pleasure to thank the many colleagues, especially Nurse H M Higham, who not only made this investigation possible but also assisted us in every way, and Dr R E O Williams and Dr Patricia Jevens, of the Central Public Health Laboratory, Colindale, for phage typing many of the strains and supplying us with bacteriophages so that we could continue for ourselves

REFERENCES

Anderson, E S, Williams, R E O (1956) *J clin Path* 9, 94
Barber, M (1955) *J gen Microbiol* 13, 338
— (1958) *in* Lectures on the Scientific Basis of Medicine In the press
— Burston J (1955) *Lancet*, ii, 578
— Kuper, S W A (1951) *J Path Bact* 63, 65
— Wilson, B D R, Rippon, J E, Williams, R E O (1953) *J Obstet Gynæc Brit Emp* 60, 476
Barnard, H. F (1952) *Brit med J* i, 21
Beaven, D W, Burry, A F (1956) *Lancet*, ii, 211
Blowers, R, Wallace, K R (1955) *ibid* i, 1250
Chadduck, W M, Alexander, D C, Trefers, H P (1954) *Proc nat Acad Sci* 40, 1064
Duthie, E S (1957) Symposium on Hospital Coccal Infections (Association of Clinical Pathologists and Medical Research Council), p 23
Frisby, B R (1957) *Brit med J* ii, 506
Garrod, L P, Waterworth, P M (1956) *ibid* ii, 61
Gillespie, W A, Alder, V G (1957) *Lancet*, i, 632
Hobson, D (1954) *Brit med J* i, 236
Hoffstadt R E., Youmans G P (1932) *J infect Dis* 51, 216
Howe, C W (1954) *New Engl J Med* 251, 411
McDermott, W (1956) *Brit med J* ii, 837
Pinner, M, Voldrich, M (1932) *J infect Dis* 50, 185
Rountree P M, Freeman, B M (1955) *Med J Aust* ii, 157
Thomson E F, Rountree, P M, Freeman, B M (1956) *Antibiotics Ann* (1955–56) p 63
Wise, R I Voigt A E, Collin, M V, Cranny, C L (1955) *Arch intern Med* 95, 419
Williams, R E O, Rippon, J E. (1952) *J Hyg, Camb* 50, 320

TONGUE BIOPSY

A TECHNIQUE USING A RIGID SUCTION TUBE

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There have been many excellent reports of the macroscopic appearance of the tongue in disease (Sircus et al 1957), particularly of its value as an indication of deficiency of riboflavine, nicotinic acid, and protein (Spies et al 1938). In pernicious anæmia, the appearance of the tongue improves after the administration of cyanocobalamin vitamin B^{12} (Brown 1949)

In Australia Bolton and his colleagues have made valuable studies of the appearance of the tongue in malnutrition and pregnancy (Bolton 1958, Bolton and Forster 1958) and have correlated the changes with the neurological findings (Bolton 1955) and the level of serum-albumin (Gandevia and Hossack 1955)

A survey of the recent literature available to us has revealed no such studies based on biopsies of the epithelium of the tongue, though tongue biopsy has been used to investigate local lesions such as cancer

Our purpose here is to describe our experience with tongue biopsy, with special reference to a new biopsy tube designed in our unit It is a modification of the flexible suction gastric biopsy tube first described by two of us (Wood et al 1949)

Only a limited report can be given of the histological findings a full discussion will be published when further data become available, especially concerning serial biopsies in 1 patient

The study was begun by using fine scissors to cut small fragments of epithelium, but this proved unsatisfactory, especially when the central zone was being examined It was difficult to obtain sufficient depth without causing the patient subsequent discomfort by exposing too great an area After 17 biopsies had been cut with fine scissors with only moderate success it became apparent that a suction biopsy tube would be preferable, because it would remove a full depth of epithelium and some underlying substantia propria from a limited area Following a number of trials a rigid suction tube was designed which produced suitable fragments

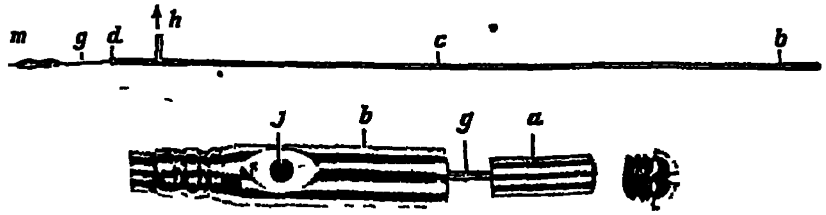

Fig 1—Rigid suction-tube for tongue biopsy, with details of operating head

The Tube

The tube† (fig 1) consists of a cylindrical knife (a) and head (b) about 3 cm long and 6 mm outside diameter rigidly mounted on one end of a stainless-steel tube (c) 41 cm long and 4 mm in diameter The proximal end is fitted with a suction-tight gland (d) and a lateral tube (h) through which suction is applied The knife (a) 11 mm long and 4 mm diameter has a proximal cutting edge and is screwed on to the end of a 19-gauge spring steel wire (g), which traverses the length of the tube and emerges through the gland at the proximal end where it is fitted with a detachable handle (m) A hole (j), 2 mm in diameter, countersunk to a maximum diameter of 7 mm , is drilled laterally in the wall of the head (b) A terminal screw seals the end of the head, and when unscrewed allows the knife to be detached The outside wall of the head, diametrically opposite the hole, is marked to permit accurate location of the hole on the tongue On operation a suction of 40 cm Hg is applied, a small fragment of tongue is sucked into the hole (j) and is cut off when the knife is operated

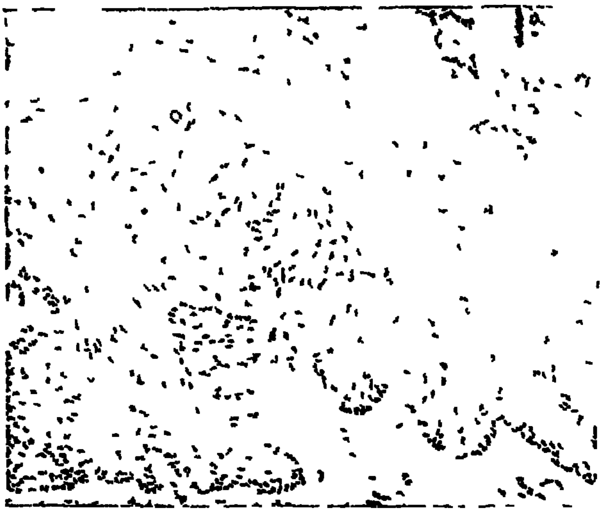

Fig 2—Biopsy of normal tongue Actively proliferating basal cells lie between primary and secondary papillæ in substantia propria , prickle cells are numerous , superficial squamous cells have formed filiform papillæ, and groups of cocci are visible on desquamating cells in upper right-hand corner (Hæmatoxylin and eosin × 150)

Technique

The patient lies with his head supported by a pillow The operator sits on his left and grasps the tip of the protruded tongue after wrapping it in gauze The area selected is swabbed with benzalkonium chloride and alcohol, and then 3% cocaine in 1 10,000 adrenaline A fine needle (26 gauge) is inserted at an angle of about 30° and 0 3 ml of procaine 2% solution is slowly injected below the epithelium

The biopsy tube is applied lightly and accurately over the area of anæsthesia, the position of the lateral hole being indicated by the location mark on the instrument The proximal end of the tube is held by an assistant, who depresses the operating handle to open the lateral hole, applies negative pressure to suck in the fragment, and immediately pulls up the knife blade This operation may be repeated over a neighbouring site to obtain a second fragment The fragment is retrieved by removing the terminal screw and unscrewing the cylindrical blade A fragment remaining in the cylinder may be blown out by a stream of air

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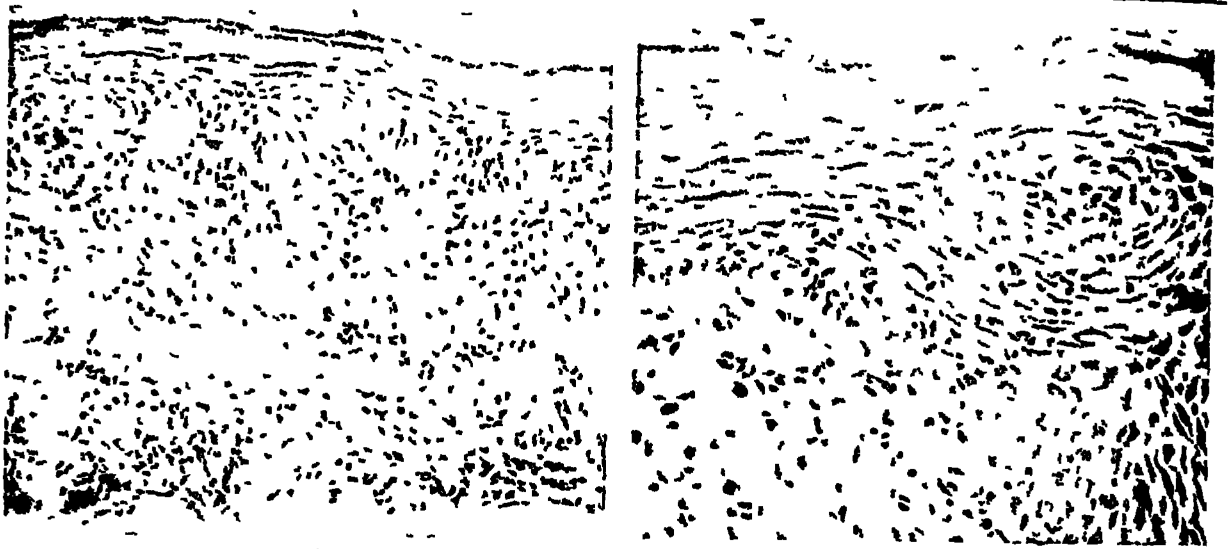
* Working with the aid of a grant from the National Health and Medical Research Council of Australia

† This biopsy tube is made by H A Taylor and Son (Surgical) Pty Ltd, 44, Macfarlan Street, South Yarra, Melbourne, Victoria, Australia



(A) (B)

Fig 3—Tongue biopsy in atrophic glossitis Woman, aged 45, with chronic hepatitis, malnutrition and recurrent glossitis Tongue was painful, ulcerated, red, and smooth A, gross thinning of epithelium and loss of filiform papillæ, while primary and secondary papillæ have disappeared, heavy inflammatory infiltration of substantia propria and epithelium (Hæmatoxylin and eosin × 300) B, thin basal and prickle-cell layers of epithelium and infiltration of substantia propria and penetration of epithelium by lymphocytes (Hæmatoxylin and eosin × 600)

The fragment is immediately fixed in 10% formol saline and when embedded in paraffin, oriented to obtain a vertical section of the mucosa

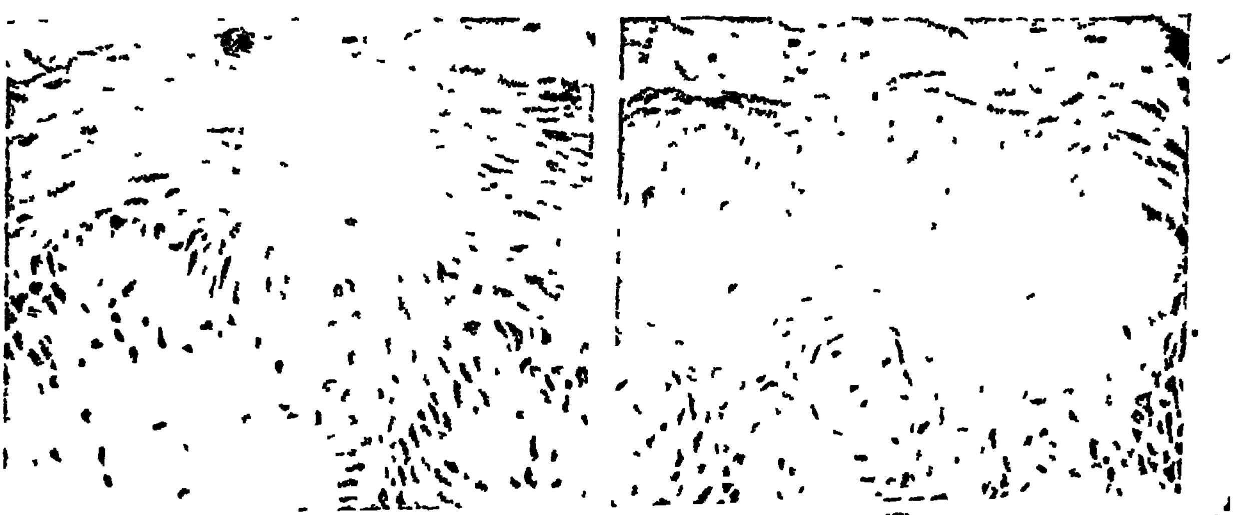
Results

With this model 50 successful biopsies have now been made at 53 attempts on 40 people whose tongues either appeared normal (17) or showed atrophy or inflammation (33) The specimen was usually taken from an area about 2 cm from the tip and mid-way between the median groove and the lateral edge On 18 occasions two fragments were obtained from neighbouring sites 6 people had further biopsies a week or more later, 1 having 4 biopsies, 2 having 3, and 3 having 2 The 3 failures were all in people with considerable atrophy of the epithelium—1 with pernicious anæmia, 1 with recurrent glossitis, and 1 with malnutrition and atrophic glossitis In 2 of these, small fragments were subsequently obtained by fine scissors, but this was difficult and caused relapse in the case of ulcerative glossitis

In the 50 successful biopsies when the suction tube was used, no major discomfort was felt either during or after the operation Most subjects reported no discomfort, a few had slight soreness of the tongue for twenty-four hours

Pathology of Biopsy Fragments

Biopsies of the anterior upper surface of the normal tongue presented an appearance in keeping with standard descriptions (Maximow and Bloom 1948), the three layers (superficial squamous, prickle, and basal) being clearly identified Certain regions showed evidence of more rapid proliferation of the basal cells, these cells forming a layer three to six cells thick and being cuboidal



(A) (B)

Fig 4—Tongue biopsy, showing glossal atrophy Woman aged 51, with untreated pernicious anæmia Tongue was red, smooth and atrophic A, considerable thinning of epithelium Basal layer is only one or two cells in depth and few prickle cells remain There is thin smooth superficial squamous-cell layer (Hæmatoxylin and eosin × 600) B, after treatment with vitamin B_{12} for six weeks Basal-cell proliferation is more pronounced, numerous prickle cells are present Keratohyaline granules are visible in superficial squamous-cell layer (Hæmatoxylin and eosin × 600)

or low columnar in shape, with darkly staining oval nuclei and scanty cytoplasm (fig 2) More superficially the cells were prickle-cell in type, forming a layer about six cells thick Here the cells were oval or spindle-shaped, with paler staining and irregularly shaped nuclei, and peripheral intercellular bridges visible under higher magnification More superficially again there was a squamous-cell layer, often containing keratohyaline granules At the surface these cells formed filiform papillæ, whose surface was roughened by desquamating cells which often contained groups of cocci (fig 2) Biopsy on "furred" tongues showed excess amounts of this superficial cellular material and cocci Over fungiform papillæ the surface was smooth

In regions where basal-cell proliferation appeared less active, the basal-cell and prickle-cell layers were only one or two cells in depth, while the squamous layer was thin and smooth Under these areas the substantia propria projected up to form primary and secondary connective tissue papillæ These normally contained some thin-walled capillaries and an occasional fibroblast and mononuclear cell (fig 2)

When there was macroscopic glossal atrophy good general correlation was found with the histological appearances Here the areas of slower basal-cell proliferation were increased and tended to coalesce, with a corresponding reduction or disappearance of the regions of rapidly multiplying basal cells (fig 3) This produced a thin smooth mucosa in which filiform papillæ had disappeared all three layers of the stratified squamous epithelium were reduced in width and the primary and secondary connective-tissue papillæ were absent

Biopsy of a tongue showing moderate macroscopic atrophy revealed loss of the filiform papillæ and decrease in prickle cells, with gross macroscopic atrophy there was thinning of all epithelial layers and absence of the papillæ of the substantia propria

With atrophy of the epithelium the coccal colonies disappeared, possibly because of a decrease in the supply of nutritional factors afforded by the normally desquamating cells Such a decrease in the normal bacterial flora and a reduction of the mechanical barrier may predispose the tongue to bacterial infection and inflammation

In a case of pernicious anæmia with considerable atrophy of the epithelium, the biopsy was repeated after six weeks of treatment with vitamin B_{12} (fig 4) Even allowing for slight variation in the cutting angle of the sections, there was an increase in the thickness of the basal and prickle-cell layers, and keratohyaline granules had formed in the squamous layer The connective-tissue papillæ were also increased in depth

The only inflammatory changes observed in this series were an increase in the lymphocytes, plasma cells, and mononuclear cells in the substantia propria Lymphocytes were frequently seen penetrating the epithelium, lying in small vacuoles between the cells (fig 3)

Discussion

In this limited experience there was good correlation between the appearance of atrophy of the tongue and the biopsy findings When the tongue appeared normal, the biopsy revealed stratified squamous epithelium which could be seen as a plate of proliferating basal cells' In some areas proliferation appeared to be more rapid than in others, producing an uneven epithelial layer With the development of atrophy the basal-cell proliferation became slower and more even, thus producing a thin smooth epithelium

In 1 case of pernicious anæmia the administration of vitamin B_{12} was followed by a cellular response towards a more normal epithelium—a change parallel to that seen in other proliferating cells such as the hæmopoietic bone marrow, but absent in the gastric mucosa (Doig and Wood 1950, Finckh and Wood 1953)

It may well be that studies based on biopsy of the tongue will throw further light on the degenerative processes in various diseases, especially with regard to the cellular changes Serial biopsies on a single patient may also produce critical evidence of the value of various therapeutic measures

Summary

A rigid suction tongue-biopsy tube is described

50 successful biopsies were made in 40 people whose tongues either appeared normal or showed atrophy or inflammation There was no major discomfort either at operation or later

The fragments obtained were suitable for histological examination There was a full depth of epithelium with some underlying substantia propria When the tongue appeared atrophic there was good correlation between macroscopic and histological appearances

Studies based on biopsy of the tongue may throw further light on the degenerative processes in various diseases, especially with regard to the cellular and tissue changes Serial biopsies may aid in assessing the value of treatment

Our thanks are due to the members of the honorary medical staff of the Royal Melbourne Hospital for sending patients for examination, to Miss E Earle for skilfully preparing the histological specimens, and to Mr R Inglis, photographer to the Royal Melbourne Hospital, for providing fig 1

REFERENCES

Bolton, J H (1955) *Med J Aust* i, 10
— (1958) *ibid* i 5
— Forster, F (1958) *ibid* (in the press)
Brown A (1949) *Brit med J* i, 704
Doig, R. K. Wood, I. J (1950) *Med. J Aust* ii 565
Finckh, E S., Wood, I J (1953) *Gastroenterology*, 25, 48
Gandevia, B, Hossack, D (1955) *Med J Aust* i, 344
Maximow, A A., Bloom, W (1948) A Textbook of Histology, p 353 Philadelphia.
Sircus, W Church, R., Kelleher, J (1957) *Quart J Med* 26, 235
Spies, T D Cooper C., Blankenhorn M A (1938) *J Amer med Ass* 110, 622
Wood, I J, Doig, R K. Motteram, R Hughes, A (1949) *Lancet*, i, 18

COMPOSITION OF PLASMA CHOLESTEROL ESTER

IN RELATION TO CORONARY-ARTERY DISEASE AND DIETARY FAT

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THE fatty acids of cholesterol esters (C.E.F.A.) in plasma are highly unsaturated (Bloor et al 1938, Kelsey and Longenecker 1941, Michalec 1956), the mean iodine value (I.V.) in man being 157 8 in Bloor's series Prominent among the unsaturated C.E.F.A. are linoleic and (to a lesser extent) arachidonic and linolenic acids, which are essential in that they cannot be synthesised in the mammalian body from saturated fats or acetate and that pathological changes take place in some animals fed on diets deficient in them Many vegetable oils containing a preponderance of these fatty acids have the property of lowering the serum-cholesterol (Ahrens et al 1955), Frishley et al 1955, Bronte-Stewart et al (1956), appar-

FATTY ACIDS OF CHOLESTEROL ESTER OF PLASMA IN NORMAL BANTU AND WHITE SUBJECTS, AND IN PATIENTS WITH CORONARY-ARTERY DISEASE (EXPRESSED AS MEAN AND STANDARD DEVIATION)

—	Bantu	White	Coronary-artery disease
Ester cholesterol (mg per 100 ml)	91 (32)	141 (12)	151 (31 5)
Iodine value	179 (26 5)	160 (34 5)	136 (35 6)
% Linoleic	55 4 (10 8)	53 2 (10 7)	40 6 (15 5)
% Linolenic	8 6 (4 3)	5 1 (2 5)	5 4 (2 8)
% Arachidonic	13 6 (4 9)	9 5 (2 3)	7 6 (3 0)
% Pentaenoic	1 2 (0 8)	1 4 (0 5)	2 1 (1 0)
% Hexaenoic	3 2 (2 0)	2 5 (2 7)	2 8 (2 7)
% Saturated + oleic	18 0	28 3	41 5

ently by accelerating the catabolism of this sterol to bile acid (Lewis 1957, 1958)

Studies on *total* serum fatty acids have been reported from several centres Wiese et al (1956) have found that trilinolein feeding increases the percentage of linoleic and arachidonic acids Hammond and Lundberg (1955), comparing Guatemalans on low fat intakes, atherosclerotic subjects, and blood-bank donors, demonstrated lower percentages of linoleic and arachidonic acids, but a probable higher percentage of linolenic acid, in the atherosclerotic group Also employing the technique of alkali isomerisation for the analysis of polyunsaturated fatty acids, Antonis (1957) reported a lower percentage of linoleic acid in atherosclerotic patients than in normal white subjects, while Bantu mine labourers had far higher percentages of linoleic and arachidonic acids On the other hand, James et al (1957) were unable to demonstrate an abnormality of serum fatty acids in patients with coronary-artery disease, using vapous phase chromatography as the analytical procedure In interpreting these studies it should be noted that total serum fatty acids may not represent a homogeneous physiological entity

These interrelationships suggested an investigation into plasma C E F A composition in coronary-artery disease, and as a corollary, in Bantu subjects, whose susceptibility to this condition is exceedingly low * Feeding experiments have been carried out to ascertain whether plasma C E F A were affected by the nature of the dietary fat C E F A from atheromatous coronary arteries have also been analysed

Twelve white patients who had had one or more cardiac infarctions were studied They were ambulant, and were selected in that their dietary habits (so far as could be ascertained) had not been changed after their illness, at the time of the survey none was receiving anticoagulant therapy Twelve Bantu subjects were investigated they were clinically normal, and care was taken to exclude any whose dietary and other customs might have been modified by urbanisation Eight white subjects, clinically and electrocardiographically normal, served as controls The samples were analysed without prior knowledge of the group to which they belonged The mean ages of the three groups were 40, 35 5, and 48 years respectively

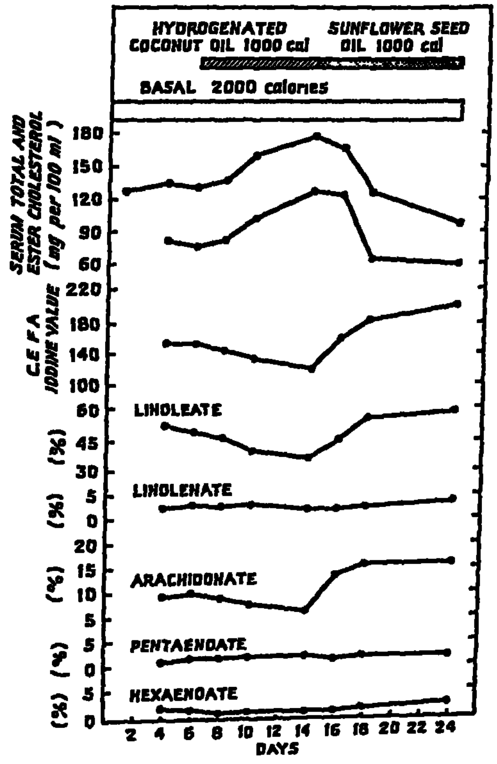
Plasma was extracted within one hour of venesection, using ten volumes of methylal-methanol 4 1 (Delsal 1944) The total lipid was fractionated according to the procedure of Fillerup and Mead (1953) by chromatography on silica gel, previously deactivated and washed with methanol and ether containing 0 1% hydroquinone to remove adsorbed oxygen, and finally washed with petroleum ether Saponification of cholesterol esters was carried out at 35°C using potassium *tert*-butoxide, cholesterol was removed, the soaps were hydrolysed, and the fatty acids extracted conventionally Fatty acids were determined by electrometric titration to pH 9 0 with 0 01N ethanolic potassium hydroxide, assuming a mean molecular weight of 286 A micro-bromine addition procedure (Trappe 1938) provided a measure of overall unsaturation, and poly-unsaturated fatty acids were characterised and determined by the alkali isomerisation technique of Herb and Riemenschneider (1953), saturated plus oleic acids were computed by difference All operations were performed in a nitrogen atmosphere

As the table shows, C E F A iodine values were highest in the Bantu group and lowest in the patients with coronary-artery disease This was due mainly to differences in linoleic and in arachidonic acid percentages, and reciprocally in saturated (mainly palmitic by paper chromatography) plus oleic acids The coronary group had the highest and the Bantu the lowest total lipid levels

Application of the t test showed that the differences between the C E F A iodine values of the three groups were *significant at the 5% level*, that between the Bantu and coronary groups being almost significant at the 1% level The differences between the percentages of arachidonic acid were also significant at the 5% level, but linoleic acid differed significantly only between white and coronary and between Bantu and coronary groups

Feeding experiments were carried out on two normal Bantu subjects in the metabolic ward The basal diet contained 5 g of fat Dietary oils were substituted isocalorically for carbohydrate Administration of hydrogenated coconut oil (I V 6) and sunflower-seed oil (I V 135) was shown to produce wide variations in C E F A unsaturation In the experiment shown in the chart, the C E F A iodine value fell to 122 during coconut-oil feeding and rose to 199 when this was replaced by sunflower-seed oil Linoleic and arachidonic acids were the most labile Administration of the latter oil elevated the percentage of these acids in C E F A before the serum-cholesterol fell significantly

Atheromatous coronary arteries were found to contain relatively saturated C E F A Using similar analytical techniques, a mean I V of 64 was obtained in material



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* Several other biochemical, hæmatological and clinical modalities were investigated by Dr C Merksey, Dr H Gordon, Dr R Lackner, and Dr H Nossel These will be published separately

from four autopsies, 81% of the C.E.F.A. comprised saturated and oleic acids, the percentages of acids with two, three, four, five, and six double bonds being 11, 3.3, 3.6, 0.31, and 0.43 respectively This finding agrees with the observations of Schönheimer (1926) and Keegan and Gould (1953), who found the predominant fatty acids in human aortic plaques to be stearic, palmitic, and oleic. There is a possible parallel to this example of a higher degree of saturation of tissue-C.E.F.A in comparison to circulating esters Alfin-Slater et al (1954), working on rats, have found that deficiency of essential fatty acids leads to deposition of cholesterol and fat in the liver Achaya et al, cited by Deuel (1955), have shown further that under these conditions liver-cholesterol, normally esterified to a large extent with oleic acid, becomes bound to saturated acids

Using the data obtained in the survey, regression equations were calculated for plasma ester-cholesterol against C.E.F.A. iodine value, and against the percentages of linoleic, arachidonic, and palmitic plus oleic acids in plasma C.E.F.A. The correlation coefficients for the same data were all significant at the 5% level by Fisher's z test. This corresponds to the observation, in the feeding experiments, of a reciprocal relation between plasma ester cholesterol and the content of certain unsaturated fatty acids in plasma cholesterol esters

The regression lines for these sets of variables were somewhat dissimilar in the three groups studied, but the differences in slope were not statistically significant

Thus the proportion of saturated and oleic acids in the C.E.F.A. was far higher in atheromatous plaques than in plasma, while in plasma itself it was highest in subjects with established coronary-artery disease and lowest in the Bantu In the light of these studies it seems possible that a primary effect of dietary unsaturated fats is to increase the unsaturation of circulating cholesterol esters, perhaps rendering their solution in plasma more stable or making the cholesterol more susceptible to catabolism to bile acid However, the high concentration and probable functional importance of poly-unsaturated fatty acids in intracellular organelles (Kretchmer and Barnum 1951) have also to be considered Feeding a diet rich in such acids may conceivably facilitate certain metabolic activities, including cholesterol catabolism

This study was carried out as part of the programme of the Clinical Nutrition Research Unit supported in the University of Cape Town by the South African Council for Scientific and Industrial Research It is a pleasure to acknowledge my indebtedness to Dr H Gordon for his invaluable assistance in selecting the clinical material for the survey, to Prof J F Brock and Dr C Merskey for their encouragement, and to Mrs L Rose-Innes for technical assistance

REFERENCES

Ahrens, E. H, Jr, Tsaltas, T T, Hirsch, J, Insull, W, Jr (1955) *J clin Invest* 34 918

Alfin-Slater R. B, Aftergood, L., Wells, A. F., Deuel, H. J, Jr (1954) *Fed Proc* 13, 174

Antonis, A. (1957) Paper read at Conference on Essential Fatty Acids, Oxford July 1957

Bloor, W R., Blake, A. G, Bullen, S S (1938) *J Allergy* 9 227

Bronte-Stewart, B Antonis A., Eales L. Brock, J F (1956) *Lancet* i, 523

Delsal, J L. (1944) *Bull Soc Chim biol, Paris*, 26, 99

Deuel H J, Jr (1955) *Fed Proc.* 14 639

Fillerup, D L., Mead J F (1953) *Proc. Soc. exp Biol Med* 83 574

Friskey R. W Michaels, G D Kinsell L. W (1955) *Circulation* 12, 492.

Hammond E. G, Lundberg W O (1955) *Arch. Biochem Biophys* 57, 517

Herb, S F Riemenschneider R. W (1953) *Anal Chem.* 25 952.

James A T Lovelock J E., Webb, J Trotter, W R. (1957) *Lancet*, i, 705

Keegan, P Gould R. G (1953) *Fed. Proc.* 12, 225

Kelsey, F E. Longenecker, H E. (1941) *J biol Chem* 129 727

Kretchmer, N Barnum C. P (1951) *Arch. Biochem Biophys* 31, 141

Lewis B (1957) Proceedings of the Research Forum of the University of Cape Town. Abstracted in *S Afr med J* 1958, 32, 65

— (1958) *Lancet* i 1090

Michalec C. (1956) *Biochim biophys Acta* 19, 187

Schönheimer R. (1926) *Z physiol Chem.* 160, 61

Trappe W (1938) *Biochem Z* 296 180

Wiese H F, Hansen, A. E., Adam, D J D., Baughan, M. A. (1956) *Fed Proc.* 15, 577

CHRONIC DISSECTING ANEURYSM OF THE AORTA DIAGNOSED BY AORTOGRAPHY

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Dissecting aneurysms of the aorta usually run a rapid clinical course and are often fatal within twenty-four hours Shennan (1934) examined 143 recent dissecting aneurysms and found that 84% of the patients died within the first week. However, it is now well recognised that patients occasionally recover from the initial episode and may live for many years with the condition unrecognised According to Drury (1955), who reported 2 such cases, most of the healed aneurysms described fell into a surprisingly uniform pattern. Most are " double-barrelled aortas " extending from the distal part of the arch of the aorta to the bifurcation They show clear evidence of patency, and their sacs become lined with endothelium and may contain varying degrees of atheromatous change

It is difficult to assess the real frequency of healed aneurysms of the aorta Weiss et al (1940) estimate that one dissecting aneurysm in ten is apt to heal

It is clear from the literature that a correct diagnosis of chronic dissecting aneurysm is rarely made during life Even less commonly is positive proof of the diagnosis obtained before necropsy For these reasons the following case is considered worthy of recording

Case-report

On Oct. 8, 1952, a painter, aged 43, was seized with a severe pain in the chest and back while drinking a cup of tea. The pain was continuous but was worse with breathing He remembered having a similar pain twenty years before, after an accident. On admission to University College Hospital, he was pale, and in obvious pain, but was not shocked. The blood-pressure was 130/80 mm. Hg, but rose within a few hours to 210/130 and thereafter remained at about this level The pain gradually lessened, and after a week, with a morning pyrexia, the patient seemed fairly well again. An electrocardiogram on admission and another next day proved normal.

Blood-culture during the first twenty-four hours grew a non-hæmolytic streptococcus A leucocyte-count of 14,000, with 82% polymorphs, was found on admission. The diagnoses considered were small dissecting aneurysm, spontaneous perforation of the œsophagus, and Bornholm disease. Several radiographs of the chest, taken after admission, showed a slight increase in the breadth of the mediastinum, which was thought to be significant. A clinical diagnosis of dissecting aneurysm was made His recovery was uneventful, and he was discharged perfectly fit four weeks after admission, but without a firm diagnosis

He returned home and to his work, and remained well until the following year when he collapsed and was admitted to Hillingdon Hospital Shortly afterwards he had a large hæmatemesis He was treated medically and recovered well Duodenal ulceration was diagnosed after a barium-meal examination. He remained well on an ulcer regime until 1956

During 1956 he developed a bloated feeling in the abdomen, and was found to have a pulsatile abdominal swelling which was thought by Mr J R. Elder to be an aortic aneurysm.

On admission to St. Mary's Hospital on June 26, 1956, he appeared to be in fairly good health The pulsatile abdominal swelling could easily be felt below and to the left of the umbilicus The blood-pressure was 220/120, and the apex beat was displaced to the left. No hypertensive changes were noted in the fundi, and the urine contained no albumin The blood-urea was 36 mg per 100 ml On June 29, lumbar aortography was performed by Dr D F Reynolds of the radiological department, to define the exact site and size of the suspected aneurysm, and showed the rather unusual appearances illustrated in fig 1 These gave rise to some controversy but were finally attributed to a dissecting aneurysm It was thought that the needle point had entered the sac of the aneurysm which was clearly visualised, and that the contrast medium was then entering the true lumen of the aorta, which was also shown, though less clearly, on the serial films It was suggested that the diagnosis could be confirmed and the true lumen of the aorta adequately shown by retrograde catheterisation from the femoral artery, and this was done by one of us (D S) on July 25 The aorta was readily catheterised, and contrast injections showed the appearances illustrated in fig 2 These confirm that the true lumen of the aorta was separate from the lumen of the dissecting aneurysm demonstrated by lumbar aortography and was somewhat compressed by it They suggested that the dissecting aneurysm began somewhere in the region of the aortic arch and finished in the region of the common iliac arteries They also suggested that the dissecting aneurysm was interfering with the blood-flow to the kidneys

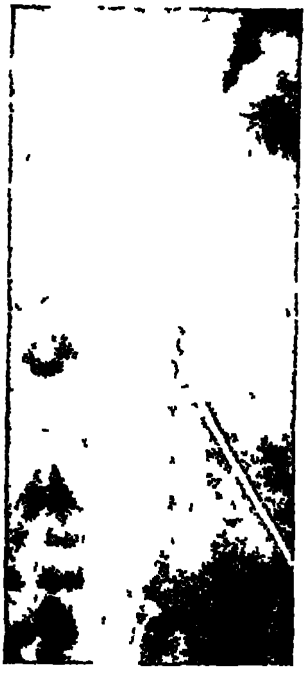


Fig 1—Lumbar aortogram *The needle has entered the sac of a dissecting aneurysm, which is shown extending up into the thorax Contrast medium has passed from the aneurysm into the true lumen of the aorta, which is shown lying parallel to the dissecting aneurysm and to its left*

This interesting finding raised the possibility that the hypertension might have been caused by the encroachment of the dissecting process upon the lumen of one or both the renal arteries Further investigation of the renal function showed that both kidneys seemed to function adequately It was thought, however, that if his blood-pressure could be reduced it would improve the long-term prognosis, and hypotensive therapy was therefore instituted

When seen in December, 1957, the patient remained well and free from fresh symptoms

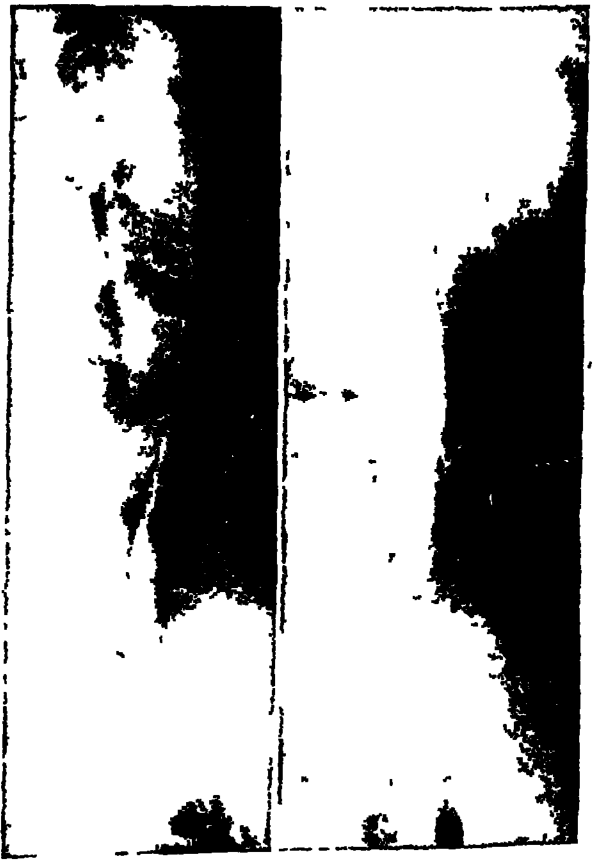
Discussion

The diagnosis of dissecting aneurysm, rarely made during life, may be suggested on a plain radiograph by progressive enlargement of the aortic shadow on serial films of the chest This possibility was raised in our patient on his original admission at University College Hospital However, this is a sign that must be treated with caution and can be misleading Great care must be taken that the serial films are exactly comparable One of us has seen a case where the diagnosis was confidently suggested on plain X-ray grounds, but not confirmed at necropsy The apparent mediastinal increase in width was then presumed to be largely artefact

The use of contrast media will allow positive proof of the diagnosis, but few previous cases can be found where these have been used In a case reported by Halliday (1952), a dissecting aneurysm was demonstrated by angiocardiography in the acute stage In another case of acute dissecting aneurysm (Warren et al 1956) a positive diagnosis was obtained by an aortic catheterisation in November, 1956

In our case a positive and unequivocal diagnosis was made by contrast vascular studies not only was the aneurysm itself directly demonstrated by lumbar aortography, but the original lumen of the aorta was clearly visualised by percutaneous catheterisation from the femoral artery

The angiographic findings in this case support the opinion of Drury (1955), who held that most of the patients who survive are those with a normal ascending aorta, and that most healed dissecting aneurysms begin at or near the aortic arch He was also of the opinion that the second factor that appeared to encourage healing was the length of the aneurysm Shennan's (1934) series was quoted to support the view that short dissections rupture early, and most healed dissecting aneurysms are long and sheath-like, extending from the arch to the iliac arteries He explains this by the hypothesis that the pressure within the aneurysm will equal that of the thoracic aorta at the point of primary tear from which it arises On the other hand, the pressure within the aorta will be lowered distally by successive branching A re-entrant tear will then be favoured by the resulting pressure difference which increases with the length of the



(a) (b)

Fig 2—Aortogram by femoral catheterisation *The true lumen of the aorta is demonstrated from the aortic arch down to the iliac arteries The aorta is displaced to the left and compressed by the dissecting aneurysm (a) as are the common iliac arteries (b) There was faint filling of the dissecting aneurysm from the true aortic lumen*

Serial films show the lower limit of the dissecting aneurysm to lie in the right common iliac artery The right renal artery was not demonstrated, and only a left nephrogram was obtained aneurysm Local factors in the structure of the distal aorta and the iliac arteries may also be important

Our case appears to support this concept The primary tear is thought to lie in the region of the aortic arch and the re-entrant tear in the common iliac arteries

Summary

A case of chronic dissecting aneurysm of the aorta complicated by hypertension is reported The diagnosis was made during life by lumbar aortography and confirmed by transfemoral aortic catheterisation

Our thanks are due to Prof M L Rosenheim, of University College Hospital, for permission to use the case-notes concerning the patient's first hospital admission in 1952

REFERENCES

Drury, R. A. B (1955) *Brit med J* ii, 1114
Halliday, E. J (1952) *Austr Ann Med* 1, 68
Shennan, T (1934) *Spec Rep Ser med Res Coun, Lond.*, No 193
Warren, W D, Beckwith, J, Muller, W M (1956) *Ann Surg* 144, 530
Weiss, S, Kinney, T D, Maher, M. M (1940) *Amer J med Sci* 200, 192.

HYPOKALÆMIA FOLLOWING CHRONIC DIARRHŒA FROM OVERUSE OF CASCARA AND A DEFICIENT DIET

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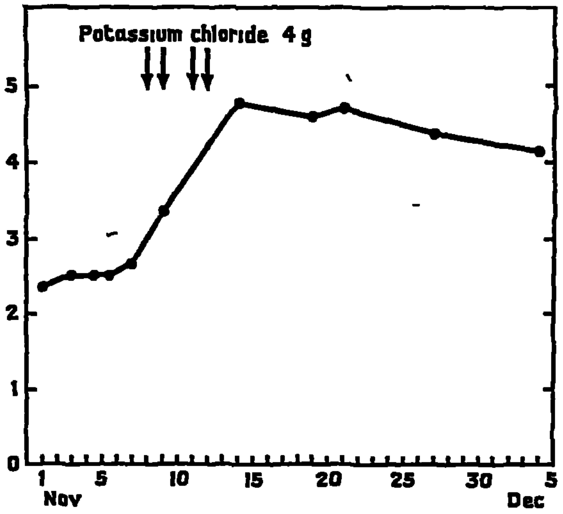
SEVERE potassium depletion and hypokalæmia following chronic diarrhœa induced by overuse of laxatives have been described in two otherwise healthy women by Schwartz and Relman (1953) In the case described here severe hypokalæmia developed in similar circumstances in a man aged 78 Associated muscular weakness of the limbs led to an initial diagnosis of cerebral thrombosis, but a routine electrocardiogram showed changes indicating hypokalæmia, which was confirmed biochemically

Case-report

A man, aged 78, came into hospital on Oct 27, 1956, because of sudden loss of power in his arms and left leg On the previous evening he had fallen asleep in a cinema and wakened with weakness of his limbs He made his way with difficulty to his lodging-house His doctor noted weakness of both arms and the left leg and sent him into hospital next day with a provisional diagnosis of cerebral thrombosis

On admission the patient still had marked weakness of his arms Abduction of his right arm and flexion of his left wrist and fingers were particularly affected His tendon-reflexes were depressed in the arms, particularly the left Power in his legs seemed, by this time, normal for one of his age and build. Next day, with no other treatment than rest in bed and an ordinary diet, he recovered power in his arms, and his tendon-reflexes returned to normal On Oct 30, 1956, routine electrocardiography showed changes indicating hypokalæmia The serum-potassium level was 2 3 mEq per litre The patient had not had any previous episodes of this kind, but he had had transient weakness of his fingers during the week before admission to hospital

Further observation showed that he was a depressed lonely old man He had retired from labouring nine years previously He had left his native Ireland as a young man and had no relations, and few friends in Scotland He felt unwanted and had the idea that the people in his lodging-house complained of an unpleasant smell emanating from him He thought this was the result of food rotting inside his body, and that it could be corrected by frequent aperients Consequently he had for months, if not years, taken two cascara tablets three times each day He was secretive and evasive about his bowel movements, particularly after he was forbidden laxatives, and refused to cooperate in the collection of specimens He regarded himself as constipated if he had fewer than three bowel movements in the day



Serum-potassium *levels, showing effect of increased intake of* potassium

Diet—He was vague about his dietary habits He had bought and prepared his own food for years and seemed to have lived for a considerable time on a diet consisting largely of bread, margarine, and tea He seldom, if ever, ate butcher's meat, bacon, or fish He may have had up to three eggs in a week He was 5 ft 8 in tall and weighed 7 st 10 lb when he came into hospital He was thin but showed no overt sign of malnutrition

Investigations—His urine was acid On repeated testing it was free from albumin, casts, and red cells and contained only an occasional leucocyte, it was sterile on culture on four occasions, its specific gravity was 1 008–1 012 The urinary excretion of potassium was 151 4 mg in twenty-four hours on Nov 7, 1956, and 72 8 mg on Nov 9 Potassium chloride 1 g four times daily by mouth was given from Nov 8 to Nov 12, and the urinary excretion of potassium in twenty-four hours was 222 5 mg on Nov 10, 363 mg on Nov 14, and 685 mg on Nov 15 The serum-potassium level was initially 2 3 mEq per litre and rose to the lower limit of normal after 5 g of potassium chloride had been given and remained normal thereafter The initial serum-bicarbonate level was 43 2 mEq per litre and the initial serum-chloride level 84 0 mEq per litre, but all the levels in the serum returned to normal and the electrocardiographic signs of hypokalæmia regressed as the serum-potassium level rose (see figure) On Nov 27, 1956, the specific gravity of the urine after fourteen hours' deprivation of fluid was 1 012, two hours after the ingestion of 1 litre of water it was 1 002, corresponding figures on Dec 6 were 1 018 and 1 001 Radiography of the chest, a barium meal, a barium enema, and intravenous pyelography showed no significant abnormality Fat balance was attempted but had to be abandoned because the patient resented being forbidden purgatives On Oct 30, 1956 the erythrocyte-sedimentation rate was 14 mm at the end of one hour (Westergren), the white cells numbered 8000 per c mm, Hb 11 9 g per 100 ml The Wassermann reaction of the blood was negative The fasting blood-sugar level was 90 mg per 100 ml The levels of acid and alkaline phosphatase, calcium, and inorganic phosphate in the serum were normal

Subsequent course—The patient's general health improved gradually, and after he had been six weeks in hospital he had gained $1^1/_2$ stone in weight Unfortunately, although his physical health was now quite satisfactory for a man of his years, his mental depression did not improve He was admitted to a mental hospital in May, 1957 He died suddenly, apparently of coronary thrombosis, two months later There was no necropsy

Discussion

In health potassium is excreted by the kidney and, to a lesser extent, by the bowel Depletion of potassium is usually the result of increased loss by one of these channels In the present case the urinary content of potassium, when first measured, was low The only abnormalities found in the urinary system were impairment of concentrating and diluting powers, which returned to normal after the potassium depletion had been treated A renal defect of this kind is known to result from potassium depletion (Milne et al 1957)

The bowel movements had been abnormally fluid and frequent for at least some months as a result of the daily ingestion of cascara The serum-potassium level was not measured until a few days after the transient episode of paralysis Probably the serum-potassium level was then even lower than the first, and lowest, recorded reading The serum-potassium levels rose again slightly without any other treatment than the withholding of laxatives and the giving of an adequate diet The administration of 5 g of potassium chloride brought the serum-potassium level to the lower limit of normal The total potassium supplement given was 16 g of potassium chloride Thereafter the serum-potassium level remained normal without any further potassium supplements No abnormality was found in the gastrointestinal tract, and normal bowel function was restored when laxatives were discontinued It is concluded that the potassium depletion and hypokalæmia with weakness of the limbs were due to increased fæcal excretion associated with a low intake of potassium

Summary

A case of hypokalæmia with severe muscular weakness of the limbs is described

The cause of the potassium depletion is thought to have been excessive use of cascara, causing chronic diarrhœa

The dietary intake of potassium was low

The hypokalæmia was diagnosed electrocardiographically

REFERENCES

Milne, M D , Muehrcke, R. C , Heard, B E (1957) *Brit med Bull* 13, 15
Schwartz, W B , Relman, A S (1953) *J clin Invest* 32, 258

Preliminary Communication

AN ASSAY FOR INSULIN-LIKE ACTIVITY USING RAT ADIPOSE TISSUE

THE measurement of small amounts of insulin-like activity in blood and other biological fluids is still a problem A specific and sufficiently sensitive chemical, chromatographic, or immunological method, while highly desirable, is not yet available The assays so far developed are biological ones, based on insulin effects in vivo and in vitro—i e , on induced hypoglycæmia in rats and mice sensitised by endocrine manipulations,[1–3] on measurement of glucose uptake by the isolated rat hemidiaphragm,[4–6] or gas formation by mammary gland of the lactating rat [7] Because of the small maximal insulin effect (up to 2× baseline) the rat-hemidiaphragm technique demands extreme technical care if it is to achieve reproducibility and thereby adequate sensitivity Moreover, it requires the pooling of diaphragms of several animals for a given assay Hence, it has proved satisfactory in only a few laboratories

That insulin affects the metabolism of adipose tissue has been appreciated for some time,[8, 9] and more recently it has been recognised that this effect is direct, both in vivo [10] and in vitro [11]

In this laboratory [12] it has been found that insulin added in vitro to non-chilled, non-traumatised rat epididymal fat results in a fourfold increment in glucose uptake and an eightfold increase in the oxidation of glucose-1-^{14}C to $^{14}CO_2$ This observation has been adapted to measure insulin-like activity in biological fluids, and a technique has been developed [13] to measure quantities as small as 10 microunits per ml (01^{-5} or 0 00001 units per ml) Moreover, the epididymal adipose tissue from a given animal may be subdivided, giving 6 pieces (3 per side), thereby allowing comparison of insulin standards [14] and unknowns in tissue obtained *from the same animal*

PROCEDURE

Male albino rats of the Wistar strain are fed ad libitum and killed by a blow to the head and rapid exsanguination The epididymal adipose tissue is gently taken up at its base (just distal to the epididymal vessels), cut free (single cut), and, without manipulation or chilling, further cut into three equal pieces Each piece, weighing 80–200 mg , is dropped, as it is cut, into appropriate 10 ml rubber-stoppered flasks, preweighed, and containing 2 ml of plasma or Krebs bicarbonate buffer *containing gelatin 200 mg per 100 ml* and insulin in appropriate *dilutions The glucose concentration of both buffer* and plasma samples is made up to 300 mg per 100 ml containing 0 2 microcuries of glucose-1-^{14}C (1 9 ml buffer or plasma plus 0 1 ml glucose-1-^{14}C solution) The rubber stoppers are provided with two ports (glass tubing with rubber fittings) and with a small plastic cup suspended beneath one of these ports

After *reweighing, to obtain the tissue weight,* the flasks are gassed (using no 21 needles through the small rubber fittings) with 5% CO_2–95% O_2 for five minutes, the needles are withdrawn (leaving the system airtight), and the flasks are incubated for two hours at 37 6°C in a Dubnoff metabolic agitator at 72 cycles per min After incubation, using a tuberculin syringe and no 21 needle, 0 2 ml of NaOH *freshly diluted* 1 in 10 from saturated NaOH with CO_2-free water is introduced through the appropriate port into the suspended cup, and 0 2 ml 10 N H_2SO_4 is introduced into the medium After at least two hours, the contents of the suspended cup are transferred quantitatively to a weighed centrifuge tube containing $BaCl_2$, and the precipitated $BaCO_3$ is washed three times with CO_2-free water and *dried* and reweighed to give the total $BaCO_3$ *present* in the flask (usually 8–17 mg)

An aliquot of each sample is then transferred to a weighed planchette for determination of its specific activity in a proportional flow counter, giving counts ranging from several hundred to several thousand Results are expressed as counts per minute per total CO_2 (as $BaCO_3$) per 100 mg adipose tissue

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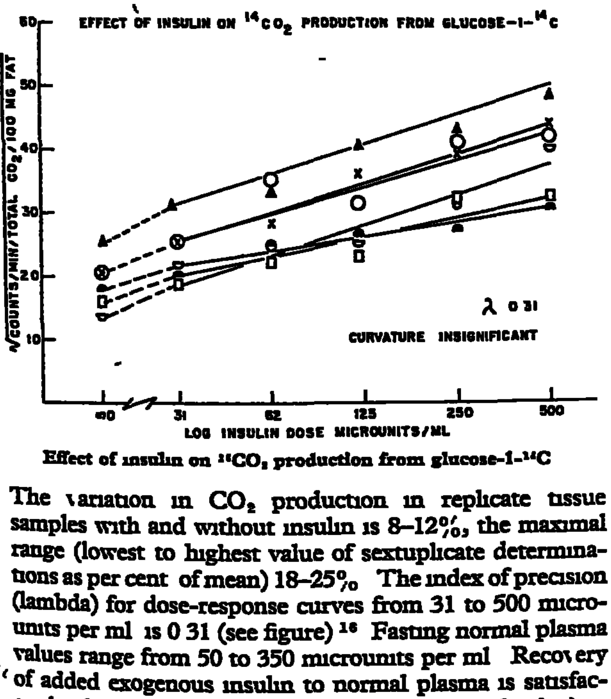
[1] Bornstein, J *Aust J exp Biol med Sci* 1950, 28, 87
[2] Anderson E , Wherry, F , Bates, R W , Cornfield, J *Proc Soc exp Biol* 1957, 94, 321
[3] Beigelman, P M , Goetz, F C , Antoniades, H N , Thorn, G W *Metabolism*, 1956, 5, 35
[4] Vallance-Owen, J , Hurlock, B *Lancet*, 1954, i, 68
[5] Randle, P J *Brit med J* 1954, i, 1237
[6] Groen, J , Kamminga, C E , Willebrands, A F , Blickman, J R *J clin Invest* 1952, 31, 97
[7] Balmain J H Cox, C P , Folley, S J , McNaught, M L *J Endocrin* 1954, 11, 269
[8] Reviewed by Shapiro, B , Wertheimer, E *Metabolism*, 1956, 5, 79
[9] Hausberger, F X , Milstein, S W *J biol Chem* 1955, 214 483
[10] Renold, A E , Marble, A , Fawcett, D W *Endocrinology*, 1950, 46, 574
[11] Krahl, M E *Ann N Y Acad Sci* 1951, 54, 649
[12] Winegrad, A I , Renold, A E *J biol Chem* (in the press)

[13] Studies supported in part by the Proctor Fund of Harvard Medical School, the Nutrition Foundation Inc , New York City, and the Adler Foundation, Inc , Rye New York
[14] Supplied through the courtesy of Dr W R Kirtley Lilly Research Laboratories Indianapolis, Indiana

The modification using the glucose uptake as indication of insulin-like activity differs in that only 0 8 ml of buffer or plasma is used, the glucose concentration is 200 mg per 100 ml, the incubation period is four hours, and sample solutions of buffer and plasma without tissue are run concurrently Aliquots of 0 5 ml are taken after incubation and glucose determinations are carried out in duplicate according to Nelson.[15] Results are expressed as micromoles glucose "taken up" per gramme adipose tissue

EVALUATION

The method using CO_2 production from glucose-1-^{14}C is preferable There are only three critical determinations —tissue weights, total $BaCO_3$ weights, and specific activity It is feasible to carry 18 flasks (3 animals) through the procedure in one and a half days, and thus to compare in each animal 4 unknowns and 2 standards, allowing an unknown to be assayed simultaneously in 3 animals The limit of sensitivity is 10 microunits per ml (132% of baseline, S E ±4%, n=20, P less than 0 01)



Effect of insulin on $^{14}CO_2$ production from glucose-1-^{14}C

The variation in CO_2 production in replicate tissue samples with and without insulin is 8–12%, the maximal range (lowest to highest value of sextuplicate determinations as per cent of mean) 18–25% The index of precision (lambda) for dose-response curves from 31 to 500 microunits per ml is 0 31 (see figure)[16] Fasting normal plasma values range from 50 to 350 microunits per ml Recovery of added exogenous insulin to normal plasma is satisfactorily obtained (within 20–25% of the predicted value)

CONCLUSION

It would appear that the epididymal fat pad of the male rat can be successfully used for the assay of insulin-like activity in biological fluids This method, in our hands, has proven more sensitive, more convenient, and perhaps more accurate, than those previously described It is, however, only a measure of insulin-*like* activity, not of insulin *per se*, and more experience is needed for a fuller appreciation of its adaptability and limitations

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Reviews of Books

Causes of Crime

Lord PAKENHAM London Weidenfeld & Nicolson 1958
Pp 197 21s

IN 1953 Lord Pakenham undertook a comprehensive inquiry into this subject at the instigation of the Nuffield Foundation it was interrupted after about a year by his public appointment, but he has now given us the fruits of his interim reflections He sets out the views of a galaxy of experts interviewed during the study, and digests the findings from a number of important British writings His conclusions are cogently argued and his opinions sound and sober, if not very controversial, and the book is easy and pleasant to read

The main theme is, inevitably, the morass of semi-knowledge wherein we flounder Lord Pakenham finds it easy to quote eminent authorities against each other on such basic points as, for example, the importance of intelligence or of mother's love Variations from place to place and from time to time make it very hard to assess statistically the recent supposed increase in crime, and international comparison is even less meaningful He points out correctly that the great majority of reasons put forward to explain this increase are, in reality, questions to which no answer yet exists unsubstantiated emotional views hold sway and facts are at a premium In his conclusions, however, he manages to avoid sinking into a paralysing "status agnosticus" He has a few suggestions to make about future research most are inevitably big undertakings and only a large well-endowed and, one might add, powerful institution could achieve them The need for the projected Institute of Criminology is inescapable and we must hope that Lord Pakenham's words will ring round the Palace of Westminster We recommend the book to a wide public, for, though it adds little itself, it could be the starting-point for many things

Die neuroallergischen Beziehungen in der Histopathologie der multiplen Sklerose

TIBOR LEHOCZKY, Hungarian Academy of Sciences, Budapest
Berlin Akademie 1957 Pp 176

Dr Lehoczky has made a thorough histological study of 20 cases of multiple sclerosis All were of the chronic progressive type, and 4 patients died during an acute exacerbation He emphasises the predilection for the optic system, and the frequency with which sclerotic foci arise under the ependyma of posterior and inferior horns, usually separated from the ventricle by a strip of intact tissue Acute inflammatory changes were found in most cases, mainly but not only in the periphery of foci The constant vascular changes (hyalinisation, delamination, œdematous filling of Virchow-Robin spaces, perivascular status spongiosus, stasis, and rarely thrombosis and the formation of microgranulomata—not only near the foci of sclerosis) are judged to be an essential part of the histological changes, and not secondary phenomena, thus, the disease involves the mesenchymal as well as the ectodermal component of the nervous system

The histological picture is compared with that of the virus forms of encephalitis and of experimental neuroallergic encephalopathy The important investigations in Russia by Margulis and his associates, who isolated three strains of virus from acute disseminated encephalomyelitis and found that the serum of patients with disseminated sclerosis could neutralise virus, are fully reviewed, but Dr Lehoczky failed to find in any of the reports of experimental infective encephalomyelitis a description of histological findings comparable with those in his human material On the other hand, the changes in the encephalitis induced by injections of brain emulsion with adjuvants, which was closely studied by Rivers, Ferraro, and others in the United States and by Lumsden in this country, closely resemble those of multiple sclerosis, and the encephalomyelitis which can follow rabies vaccination (described by Japanese workers) can be considered a link between the two diseases

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[15] Nelson N *J biol Chem* 1944, 153, 375
[16] We are indebted to Dr Mindell L Sheps, assistant professor of biostatistics, Harvard Medical School, for help and advice

Dr Lehoczky attributes multiple sclerosis to a hyperergic antigen-antibody reaction in the nervous system—a similar view to that of McAlpine, Compston, and Lumsden He believes that the hypothesis of Lumsden (that the antigen-antibody reaction takes place on the surface of oligodendrocytes and the inhibition of an antienzyme results in hydrolysis of the lipids of myelin sheaths) is not yet established No attempt is made to reconcile the experiments of Margulis et al suggesting a virus ætiology with the histopathological and experimental evidence of an allergic process

Disinfectants

Their Values and Uses W E FINCH, of the disinfectants division, Prince Regent Laboratories, London London Chapman & Hall 1958 Pp 188 30*s*

MOST clinicians and many bacteriologists are confused by the range of chemical disinfectants now available Mr Finch's book may help them to appreciate the merits and limitations of the main classes and to use them to better advantage The coal-tar derivatives are helpfully discussed at some length, and the medical reader can learn the difference between black and white fluids—though he may be bored by the details of manufacture Quaternary ammonium compounds and hypochlorites are well discussed in separate chapters, but mercurials and dyes, still much used in hospitals, get only a few lines each

The chemical information is authoritative but much of the bacteriology is elementary (the glossary includes such terms as " gram-positive ", " aseptic conditions ", and " inoculate ") A chapter on methods of testing disinfectants would have been useful, there is some information about this but it is scattered through the book The importance of using neutralisers to inactivate disinfectant carried over during testing is implied but not specifically mentioned Five plates of general views in factories and a laboratory add to the cost of the book but not to its usefulness

Where Love Is

JOSEPHINE BALLS, children's visitor London Victor Gollancz 1958 Pp 224 16*s*

ALTHOUGH relatively few children are adopted, fostered, or taken into children's homes in this country each year, they are very important for two reasons First, the amount of care they receive is an index of the social conscience The spirit of Bumbledom is by no means dead, and shows itself in exactly the way that Dickens satirised " We must not be extravagant with the ratepayers' money " is the modern equivalent of " They always cost more to keep than they're worth ", and is found in the mouths of prosperous middle-class members of committees, which the 1948 Children's Act appointed to take the place of parents who, for good reasons or bad, have become unable to keep their children All children taken into care are " deprived " children Some of them have suffered severely, and it should be a criterion of civilised society to see that restitution is made to them The second reason is that a study of deprived children and their disabilities throws much light on the needs of children as a whole, and helps us to understand many disturbances of health and behaviour which would otherwise be obscure No general practitioner or pædiatrician can afford to ignore this subject

This book is not a treatise on the law and practice of the Children's Act it is a very readable account, by an experienced social worker (child care officer in the Children's Department of Northumberland), of the reasons which led her committee to use fostering rather than nurseries for the younger children in care Fostering is much less expensive than nursery care, but happily the decision was not made in a spirit of parsimony, but because of a recognition that nurseries, no matter how devoted their staff, simply cannot offer young children the intellectual and emotional stimulus and response which is a necessity for the development of personality and even of physical health

Everyone with experience of deprived children realises that prevention, not treatment, is the real answer Most deprived children are the neglected children of inadequate parents, themselves often " deprived " The final answer is therefore to be expressed in terms of education, premarital advice, and post-natal community support The more immediate answer is to give what help is possible to a family threatened with disruption, and, for this, new statutory powers are being sought to enable children's officers to act Family help service, organised by some local health authorities, is one method The causes of neglect or non-acceptance of children, however, are many and often hard to understand For a long time to come it will be necessary to " take children into care " Miss Balls' book gives an excellent introduction to the subject

Operative Surgery

Volumes 6 and 7 Editors CHARLES ROB, M C, M CHIR, F R C S, professor of surgery, St Mary's Hospital Medical School, London, RODNEY SMITH, M S, F R C S, surgeon, St George's Hospital, London London Butterworth 1958 Pp 273 110*s* each

ORTHOPÆDIC surgery is completed in the sixth volume with a section on operations on the hand and another on amputations Plastic surgery is then completely and adequately encompassed (the form of presentation, with its reliance on illustrations, is particularly apt for this subject), and gynæcology and obstetrics follow The seventh volume presents surgery of the breast very effectively (mammoplasty is considered here, rather than in the preceding volume) In the following section on genitourinary surgery, endoscopic appearances are successfully portrayed—an important feature in the description of operations such as transurethral resection

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Modern Practice of Obstetrics (2nd ed London Baillière, Tindall, & Cox 1958 Pp 258 45*s*)—This edition of Mr D M Stern and Mr C W F Burnett's book appears six years after the first and, like its predecessor, provides brief didactic notes rather than detailed description or argument The chapter on antepartum hæmorrhage, for example, has been rewritten and now deals with the whole subject in 5 pages, which include an account of hypofibrinogenæmia The use of hypotensive drugs in pregnancy is outlined, but a critical evaluation of their usefulness would have been welcome The advances in obstetrics of the past few years are included Some lines of treatment now discredited might, with advantage, be omitted—for instance, the use of intrauterine pastes to induce therapeutic abortion and the recommendation of frequent feeds and sweetened drinks in the management of uterine inertia Today most authorities would regard both practices as potentially dangerous, though for different reasons, nor would they endorse the advice to leave a retained placenta, in the absence of hæmorrhage or infection, to be expelled spontaneously in the next few days It would be wrong, however, to underestimate, by criticising details, the value of a book with so wide a range, and many will find it a useful means of revision

Physics for the Anæsthetist (2nd ed Oxford Blackwell Scientific Publications 1958 Pp 443 60*s*)—Sir Robert Macintosh and his colleagues have always been active advocates of sound physical principles as the basis of good anæsthesia Indeed probably as much progress has stemmed from a rationalisation of the art of anæsthesia, and the consequent elimination of unscientific and undesirable techniques, as from the investigation and introduction of new drugs and methods Written to teach physics to practising anæsthetists, this book (shared with Sir Robert by Prof W W Mushin and Dr H G Epstein) makes the subject palatable, and the practical side is described and illustrated in a way that is entertaining and easily assimilated Moreover, scientific accuracy has not been sacrificed The first edition has been thoroughly revised and several additions have been made—notably, a chapter on pressure-reducing valves and four chapters on explosions, comprising nearly a third of the book That may seem a little out of proportion, but the subject of explosions, as it concerns the anæsthetist, has never been so comprehensively or authoritatively described This is an excellent book, well worth having and amply repaying repeated study

THE LANCET
LONDON 12 JULY 1958

Crime and Punishment

Lord **Pakenham**'s new book, *Causes of Crime* (reviewed on p 77), is a serious contribution to a serious subject He would be the last to claim that it is comprehensive, the gaps, particularly in foreign research, are too wide His advisers, however, must have helped him here, and the eclectic quality of the book does not detract from the value of its conclusions It is saddening to realise how elusive and contradictory is our knowledge of delinquency and crime, but the reader who is disappointed at his own imperfect understanding of the roots of crime can at least take some consolation from this book—at last he knows he does not know This reminder will do good provided it is a stimulus to renewed activity, and, although he does not discuss the matter, Lord **Pakenham**'s book is powerful ammunition for those striving for an Institute of Criminology Such an organisation would bring us into line with other countries, and, though valuable work is done at Cambridge, Oxford, the London School of Economics, the Maudsley Hospital, and elsewhere, an institute could undertake more comprehensive studies than are now possible Do approved schools, borstals, and detention centres work? Does one type of training give better results than another? Can potential delinquents be caught young, and, if so, can we abort their antisocial activity? There are half a hundred questions of great importance to which no satisfying answer exists and to which no answer is likely to be soon forthcoming Mr **Butler** seems more aware of this need than other Home Secretaries have been, but the limited expansion he has achieved at the Home Office is unlikely to meet it

The nature of the criminal act has long been the subject of bitter dispute, but, whatever may be the eternal truths underlying sin and crime, it is clear that "clinical" attitudes have slowly gained ground over the years Now it is not always just a question of quantifying the punishment to the crime Juvenile courts are taking the lead in recognising that some delinquents are disturbed rather than wicked children and need careful and individual consideration Few can doubt that a young child may reflect a disturbed home life in disturbed behaviour, one form of which may be delinquency, and most of us would surely wish to pity rather than punish this victim of evil circumstance But the delinquent child is father to the criminal man, and at what stage have we the right to change our attitude? More and more people realise that punishment per se is of less use to society and to the criminal than the creation of a person who is willing to help others instead of harming them To excuse punishment by saying it is a deterrent has a hollow ring to those acquainted with the opposition to the earliest reforms of the death penalty And to those who believe that the criminal act must ultimately come to be examined in its setting as a scientific problem of diagnosis and treatment (granting that the most effective treatment may sometimes be prison), Lord **Pakenham**'s views will be disappointing He believes that, for as far ahead as can be seen, conviction will be indissolubly connected with penalisation, and public opinion will not tolerate the idea of a penalty unrelated to the severity of the offence He holds, too, that to sever this relationship would be to "embark on a slippery slope" leading ultimately to the extermination of gypsies, Jews, Catholics, or others who may be accused of damaging the best interests of the State In company with Dr **Peter Scott**[1] and others, we look with misgiving at the proposal to incarcerate "psychopaths" up to the age of 25, even where no offence has been committed[2], but the recidivist criminal is another matter Almost any proposed reform is liable to draw criticism from somebody on the ground that it will open the way to terrible consequences But it is hard to see why, subject to rigorous safeguards, the "indeterminate sentence" should be any more a transgression against the freedom of the individual than the certification of the insane or defective is now—in fact it would probably be less so

In reality, of course, the indeterminate sentence is with us already—in the form in which it is applied to people who are found to be both criminal and insane It seems strange that a man who has repeatedly committed crimes of violence, only the thickness of the aorta maybe from murder, goes free at the end of his sentence, though every known prognostic index cries out that he will offend—and perhaps kill—again On the other hand, a patient who kills in a brief confusional or depressive psychosis is locked away for life, or at any rate for years after his recovery It is a solemn fact that men in the first group commit the spectacular murders that are in the headlines almost weekly, whereas Broadmoor patients who have been released have never killed again[3] Public opinion (that nebulous entity called upon to justify anything) may not be as averse as Lord **Pakenham** suggests to a form of indeterminate sentence

Œstrogen Measurement and Breast Cancer

Much effort is being applied to assessing and improving the effects on late breast cancer of œstrogen therapy Encouraging progress in the quantitative estimation of urinary œstrogens is referred to in the latest two annual reports of the British Empire Cancer Campaign[4] [5] and in the proceedings of a conference on endocrine aspects of breast cancer[6] Though at present we have to make do with excretion values, what we really want to know is the amounts secreted A step in this direction has been

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1 Scott, P D *Howard J* 1958, 10, 6

2 Report of Royal Commission on the Law relating to Mental Illness and Mental Deficiency, 1954–57, para 367

3 McGrath, P G *Howard J* 1958, 10, 40

4 British Empire Cancer Campaign annual report for 1957 Issued by the Campaign 11 Grosvenor Crescent, London, S W 1

5 British Empire Cancer Campaign annual report for 1956, p 340

6 Endrocrine Aspects of Breast Cancer (edited by A R Currie) Edinburgh, 1957

made by BROWN,[7] who injected known quantities of œstrone, 17β-œstradiol, and œstriol into four normal menstruating women and two men and estimated the moieties excreted in the urine The sum of these amounts was 16% of the total injected Assuming that œstrone and œstradiol or a mixture of both is the primary œstrogenic hormone in the menstrual cycle, BROWN suggests that the amount produced in the body in each twenty-four hours may be roughly estimated by multiplying the sum of œstrone, œstradiol, and œstriol excreted in that time by a factor of $^{100}/_{16}$ The result for the sample analysed was 4 8 mg during one menstrual cycle This method may provide a useful guide in substitution therapy But G F MARRIAN[6] has pointed out that present methods determine no more than 20–30% of œstrogen metabolites known to be present in urine (Do some also find their way into bile and become discharged through the bowel ?) In recent years four additional œstrogen metabolites have been found and characterised, and there are good grounds for believing that many more exist Another defect, to which attention is drawn by H BRAUNSBERG, A E KELLIE, J D N NABARRO, and D H PATEY,[4] is that estimations of œstrogens at low levels (3 μg or less) are inaccurate Available methods have been used largely to detect and measure œstrogen excretion after attempted total ablation of endogenous sources in the palliative treatment of late breast cancer The objectives have been to determine whether ablation has been complete, to correlate, if possible, the extent of fall in œstrogen excretion and clinical progress, and to obtain guidance on the most suitable form of palliation Moreover, quantitative data on œstrogen secretion in the long induction period of endogenous breast cancer will be needed in order to assess the part played by hormonal factors in causation Despite complete removal of known sources of endogenous œstrogens—the ovaries and adrenal glands—œstrogen is often found afterwards in the urine Accessory adrenals may persist, and other sources will have to be sought It is partly on account of the continued excretion of œstrone after these operations that hypophysectomy has been added to the surgical procedures, on the assumption that, as in the normal development of the breast both pituitary and ovarian hormones are required, so both sources may be needed for the growth of those breast carcinomas which respond to the absence of any one of them by temporary regression Professor ILLINGWORTH's team[4] report finding no correlation between clinical progress and the extent of the fall in œstrogen excretion after bilateral oöphorectomy and adrenalectomy, and N C SMITH, E BELL, and D LINDSAY[4] detected no œstrogens after the same operations in three-fifths of the patients in whom there was good clinical response

It is particularly difficult to account for the temporary recession of breast cancer in some postmenopausal women after administration of supplementary œstrogens If addition of these hormones is contemplated, measurement of the existing level of excretion might afford a means of predicting which patients will benefit and of determining the dose to be given A further problem exists in the reputed carcinogenic action of œstrogens By methods formerly used, no correlation was found between quantities of œstrogen excreted and established breast cancer, but such an association must be sought at a much earlier stage—perhaps for twenty years or longer This inquiry might be narrowed in two ways First, by concentrating on reputedly "precancerous" conditions, valuable information might be gained about the likely outcome of these states[8] Secondly, sufficient time has now elapsed since the introduction of synthetic œstrogens to look for evidence of any causal relationship with breast cancer P M F BISHOP and M MURRAY[4] have sought to record the results of treatment of 1029 patients for periods of at least six months Of these, only 530 could be traced and 2 only had developed cancer of target organs—in the uterus after eleven years, and in the breast after a few months' treatment with stilbœstrol (The breast tumour is unlikely to have been initiated, though it may have been promoted, by the œstrogen) A few other cases following œstrogen treatment have been recorded BUCALOSSI and VERONESI[8] recorded 2 among a group of 81 patients in whom a familial incidence had been established This observation suggests a further narrowing of the inquiry, and of œstrogen estimations, to females and males in whom a familial tendency is detected Farsighted provision for follow-up would be needed

It has long been known that the genesis of certain epithelial cytomas in animals is associated with naturally occurring or artificially altered hormone balances, and further that maintenance of the various growths of target cells depends on continuation of the same imbalance that brought them into existence Little quantitative work has been done, nor is it certainly known that these growths remain dependent once they have metastasised The exploration of this field, as was forecast by Dr CHARLES HUGGINS in his Macewen lecture in the University of Glasgow last month, may increase our understanding of many of these problems

Ventricular Septal Defect

VENTRICULAR septal defect in its typical form can usually be easily recognised, but the clinical picture varies considerably according to three principal factors —the size of the defect, the level of pulmonary vascular resistance, and the magnitude of the pulmonary blood-flow TAUSSIG[9] based her classification mainly on the site of the defect But subsequent studies suggest that it is the size of the defect rather than its position which largely determines the clinical picture, a small defect causes little hæmodynamic disturbance, whereas a large one produces large pulmonary blood-flows due to the left-to-right shunt, pulmonary arterial enlargement, and eventual heart-failure[10]

KIRKLIN et al[11] have given a detailed account of the site of defects of the ventricular septum based on 36 cases in which the defects were closed surgically. They classified defects into those related to the ventricular outflow tracts and those related to the inflow tracts. The former were subdivided into those inferior and those superior to the crista supraventricularis. The latter were divided into defects beneath the septal leaflet of the tricuspid valve and those near the apex of the muscular septum. The defects unrelated to ventricular outflow tracts were located entirely in the muscular wall of the septum, but those involving the outflow tracts (referred to as high defects), although often regarded as localised to the membranous septum, often involved a large area of muscular tissue adjacent to this region. The defects confined to the muscular septum were in the minority—11 of 38 defects in 36 patients.

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[7] Brown, J B *J Endocrin* 1957, 16, 202

[8] Bucalossi P, Veronesi, U *Brit J Cancer*, 1957 11, 337

[9] Taussig H B Congenital Malformations of the Heart New York 1947

[10] Selzer A *Arch intern Med* 1949 84, 795

[11] Kirklin J W, Harshbarger, H G, Donald, D E, Edwards, J E *J thorac Surg* 1957, 33, 45

The hallmark of the ventricular septal defect is the passage of blood from left ventricle to right ventricle—the left-to-right shunt. When the defect is small the shunt is small and symptoms are absent, the sole abnormal physical sign being the characteristic loud pansystolic murmur at the lower end of the left border of the sternum. There is no risk of heart-failure, and the sole hazard is that of bacterial endocarditis. With larger defects, symptoms of effort intolerance and respiratory infections are common, and growth may be retarded. The heart is enlarged, and death from heart-failure may result. Clinically, in such cases it is common to find hyperdynamic enlargement of the left ventricle, and to a lesser degree of the right. The characteristic loud pansystolic murmur is heard in the third and fourth interspaces at the left sternal border, an apical mid-diastolic murmur, due to increased flow through the mitral valve, is usually audible. The arterial pulse is small and slightly water-hammer in quality. The jugular venous pressure is normal unless heart-failure is present.[12] Radiologically the heart is considerably enlarged, with dilated pulmonary arteries and evidence of increased pulmonary blood-flow. The cardiogram shows greater hypertrophy of the left ventricle than of the right. Cardiac catheterisation reveals a large left-to-right shunt at ventricular level, normal arterial oxygen saturation, and normal, or near normal, pulmonary arterial pressure and resistance: the large pulmonary blood-flow is accommodated in the distensible pulmonary vascular bed without a rise in pressure. In some cases the Eisenmenger syndrome is present. This has been defined as pulmonary hypertension with high pulmonary vascular resistance and reversed shunt.[13] In such cases the left-to-right shunt is small or absent, a right-to-left shunt is present, and the clinical picture is one of extreme pulmonary hypertension with slight central cyanosis and clubbing. The mitral diastolic murmur disappears and the sound of the pulmonary valve closure is much increased. The cardiogram shows pure or dominant right ventricular hypertrophy, and the peripheral vascular markings in the lung may be reduced.[13 14] According to WOOD[13] the high vascular resistance is present from birth, and thus the clinical picture is entirely different from that of the large defect with left-to-right shunt and normal pulmonary vascular resistance. The right-to-left shunt in ventricular septal defect was originally attributed to overriding of the aorta, which received blood from the right ventricle. It is now considered that the right-to-left shunt results solely from increased pulmonary vascular resistance, which is at or near systemic level, when the aorta becomes "physiologically" overriding.[10 13] SELZER and LAQUEUR[15] suggested that there is no anatomical difference in the heart between uncomplicated ventricular septal defect and the Eisenmenger complex (better termed syndrome). The difference lies in the presence, in the latter condition, of reduced calibre of the pulmonary arterioles and consequent high vascular resistance. In any form of ventricular septal defect the aortic root may occupy its normal position, or may be overriding, or even partly or completely transposed.[15] Both WOOD[13] and SELZER and LAQUEUR[15] agree that the septal defect in the Eisenmenger syndrome measures 1 cm or more in diameter, which in the infant is of considerable size relative to the size of the heart.

A valuable study of the natural history of ventricular septal defect has been made by BROTMACHER and CAMPBELL,[16] who have analysed 75 cases. They classified these into five groups: small defects with small left-to-right shunt (3–3.5 litres per min), larger defects with a left-to-right shunt of 4–15 litres per min but with normal pulmonary-artery pressure, larger defects with considerable left-to-right shunts, and hyperkinetic pulmonary hypertension due to extreme flow rather than increased resistance, large defects with some increase in resistance but no reversal of shunt, and finally large defects with right-to-left shunt, in which the aorta is "functionally overriding." They regard the *maladie de Roger* and the Eisenmenger complex as the two extremes of a continuous series of cases of ventricular septal defect, and recommend that both eponymous terms be abandoned. Nearly three-quarters of their patients were under 20 years of age, and the sex distribution was equal, but the prognosis was considered to be worse in boys and men than in girls and women. BROTMACHER and CAMPBELL thought that the pulmonary vascular resistance tended to rise with age, in that the average age in the high-resistance cases was higher than that in the low-resistance cases. They consider that the pulmonary-artery pressure is usually high from birth, the hypertension at first is mainly hyperkinetic, but the resistance increases with age, as BLOUNT et al.[17] concluded. This is not in close harmony with WOOD's[13] view that the high vascular resistance is determined from birth. BROTMACHER and CAMPBELL[16] cite the case of a patient whose pulmonary vascular resistance was 8 units at the age of 5 years, and had risen to 23 units seven years later, but they do not believe that the pulmonary-artery pressure is likely to rise as a late complication in patients in whom it was initially normal. It may be, therefore, that the pulmonary vascular resistance is likely to rise with age only if it is initially increased These workers make valuable comments on lesions associated with ventricular septal defect Pulmonary regurgitation was diagnosed in 19 of the 75 patients, being nearly three times as common as in atrial septal defect The pulmonary pressure was increased in all save 1 Aortic regurgitation was present in 3 patients, 2 of whom died, and BROTMACHER and CAMPBELL regard this as a much more serious complication than pulmonary regurgitation The aortic arch was right-sided in 2 patients, and at least 3 had a left superior vena cava Changes of rhythm were uncommon, atrial fibrillation occurred in 1 man, and congenital heart-block in 1 woman, who was cyanotic The report refers briefly to 8 patients who were not included in the series because of a small pressure-gradient across the pulmonary valve, which was not attributed to pulmonary stenosis This "functional" gradient is now well recognised, as in atrial septal defect, in which the exact cause is not known [18]

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[12] Wood, P, Magidson O, Wilson, A O *Brit Heart J* 1954 16, 387
[13] Wood P Diseases of the Heart and Circulation London, 1956
[14] Doyle, A E, Goodwin, J F, Harrison, C V, Steiner, R E *Brit Heart J* 1957, 19, 353
[15] Selzer, A Laqueur, G L *Arch intern Med* 1951, 87, 218
[16] Brotmacher, L, Campbell M *Brit Heart J* 1958, 20, 97
[17] Blount, S G, Jr, Mueller, H, McCord M C *Amer J Med* 1955, 18, 871

The course and prognosis were analysed with reference to a further 100 patients who had not been investigated by cardiac catheterisation 11 patients died, 9 of them before the age of 25, 6 of these 9 died in childhood (1 at the age of 3 years), having enormous hearts, considerable left-to-right shunts, and heart-failure The tendency for patients with large left-to-right shunts to die in infancy is now established [19], and BONHAM-CARTER and WATERSTON [20] reported that two-thirds of a series of 200 patients with congenital heart-disease who died in infancy from acute cardiac illness did so under the age of 6 months Some of these patients presumably had ventricular septal defects, and it may well be argued that the principle mortality from this condition lies in the first year of life BROTMACHER and CAMPBELL [16] point out that if the patient survives infancy the prognosis is moderately good for fifteen years, but unless the shunt is small the outlook becomes progressively worse after this age, and few patients survive to 40 years A high infant mortality in ventricular septal defect would accord with WOOD'S [13] contention that patients in whom the high fœtal pulmonary-vascular resistance falls to normal soon after birth are in serious danger of death from heart-failure He goes further and suggests that in many cases the high pulmonary resistance of Eisenmenger's syndrome is life-saving, as it prevents the lungs being flooded with blood under systemic pressure and protects the left ventricle from the burden of the large left-to-right shunt The prognosis of the Eisenmenger complex is fair Of 35 fatal cases reported by SELZER and LAQUEUR,[15] 8 patients died in infancy, 4 between the ages of 3 and 10 years, and the remainder subsequently—1 patient living to the age of 60 19 patients survived to between the second and fourth decades, so there is a reasonable chance of a patient living to the age of 30, which agrees with BROTMACHER and CAMPBELL'S findings regarding ventricular septal defects of all types if the hazard of infancy is survived The high risk of infective endocarditis in ventricular septal defect is worth remembering it accounted for 28% of the deaths over the age of 1 year in SELZER'S [10] series, although it was not a prominent feature in the series of WOOD et al [13]

The surgical treatment of ventricular septal defect is now well established KIRKLIN et al [11] have reported excellent results in 36 cases, and the number is probably now much higher Closure requires the use of an extracorporeal circulation while the heart is opened and the defect closed, and the operation is therefore only possible in special centres. The indications for operation are a left-to-right shunt which is producing significant cardiac enlargement or effort intolerance, and early heart-failure Preferably the pulmonary pressure and resistance should be normal, but some hyperkinetic hypertension is no bar to operation, as the pressure will fall when the shunt is closed Since many patients probably die in infancy operation may prove to be most valuable when undertaken while the patient is in the first year of life The risks of operation are much greater when the pulmonary pressure and resistance are high and the shunt is reversed than in uncomplicated ventricular septal defect, and ZIMMERMAN et al [21] suggest that the pulmonary-artery pressure should ideally be below 75% of the systemic arterial pressure if closure is to be effected safely

Annotations

ASSESSMENT OF DISSEMINATED SCLEROSIS

DISSEMINATED sclerosis is diagnosed largely on the pattern of the disease in time and space But the characteristic picture of episodes of neurological dysfunction with partial or complete remission between—the episodes involving different areas of the nervous system or recurrent and increasing dysfunction of the same area—is by no means consistent A *spinal form* was early recognised as having a slowly progressive course without remissions and often without clear evidence of spatial dissemination In cerebral forms, too, an initial attack may be followed by steady deterioration In other cases a single attack is followed by complete and long-continued remission (even, occasionally, with no further recurrence) or by a series of attacks with complete remission between Other patients show increasing permanent disability after each attack In still other cases, perhaps the commonest, there is complete remission from each attack for a time and then a steadily progressive phase Examples of all these varieties have been confirmed at necropsy Thus if histological evidence of plaques of demyelinisation with profuse astrocyte infiltration and characteristic relation to blood-vessels and grey matter is accepted as pathognomonic of disseminated sclerosis, such patients must be regarded as having that disease After the first five years *all forms of the disease show* a tendency to become steadily progressive, and there is some evidence that, apart from the variations already mentioned, in general the disease may take either a relatively benign or an inexorably progressive form

These features make diagnosis and prognosis difficult and the assessment of treatment even more so If any remedy were truly curative, this could *hardly escape* detection, but if the effect were simply to slow down or modify the disease process, this would be less easily appreciated Conversely with treatment instituted around the fifth year apparent benefit might really be due to natural decline in relapses and remissions as the disease enters a chronic progressive phase

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[18] McDonald, L *Brit Heart J* 1958 20, 268
[19] Marquis, R M *ibid* 1950, 12, 265
[20] Bonham-Carter, R E, Waterston, D *ibid* 1958, 19, 589
[21] Zimmerman H A, Kay, E B, MacKrell, J, Sambhi, H P *Amer Heart J* 1957, 54, 727

Experience with the various remedies has illustrated these difficulties Of the older remedies arsenic is still advocated despite the occasional tragedy of arsenical epitheliomas Administered for periods of years, it is claimed to bring about cessation of relapses, but in many cases, however treated, relapses cease after five years Fever and shock therapies are less popular now, anticoagulants, anti-histamines, and low-fat diets, although not widely accepted, have their adherents

In this situation the carefully matched control series may be particularly helpful The recent report of Alexander et al[1] from Boston is therefore welcome They studied a group of 554 patients with disseminated sclerosis over an eight-year period and confirmed that the peak incidence is in the third decade, the disease being largely confined to the 20–40 age-group, that the frequency is greater in women than in men, that the disease tends to become less active after the first five years, and that there are probably two groups—a mild and a severe The particular merit of this report is its emphasis on the need for a quantitative estimate of disability and for assessing treatment against a control series matched not only for age, sex, length of illness, and condition at the start of treatment but also for quantitative illness record for a year before treatment Four treatments were thus investigated vitamins plus muscle adenylic acid, blood-transfusions, corticotrophin, and cortisone Of these, transfusions appeared to aid in resolution of attacks, while corticotrophin aided resolution and both prevented and reduced frequency and severity of subsequent attacks and reduced progressive disability between attacks The others had no significant effect The claim, which contrasts with the admittedly less extensive experience of other workers, that corticotrophin beneficially affects all aspects of the disease process will certainly lead to further clinical trials Let us hope these also will be so controlled that the results are meaningful

COMPLEMENT AND STIMULANT

THE Nuffield Provincial Hospitals Trust was founded in 1939 with the main purpose of coordinating hospitals and ancillary medical services on a regional basis This objective was largely fulfilled with the start of the National Health Service, but in the second decade of its short life the Trust has done work no less valuable than in the first decade

Coordination is still the principal aim, and this is reflected in the financing by the Trust of the development of group-practice and clinic centres at Harlow As a large voluntary agency, the Trust complements and stimulates official action by discovering facts on which official policy may be based, and by encouraging the practice of promising but unproved ideas In these ways such a body as the Trust can go far towards preventing the conservatism and rigidity often seen in activities paid for from Exchequer funds A report on the work in the past three years[2] remarks sensibly "that a trust must be careful not to duplicate work best done by public authorities Above all, it has a duty to be far thinking and try to interpret its objectives in relation to the requirements of the times Its policy, if not opportunist, must be as flexible as its trust deed permits " How well this Trust is succeeding is evident from the list of projects, established and new, that have gained its support

The trustees are continuing to support an exhaustive study of the administration of the National Health Service, which is being published by the Acton Society Trust New projects under organisation include further studies of hospital case-loads, to provide a basis for planning, follow-up studies of the working capacity and needs of patients discharged from hospital, and an investigation into the use of health and social services Of special interest and importance is a grant to help in planning to bring into use the new Princess Margaret Hospital at Swindon A working party is studying all aspects of the operation and will record its findings for the benefit of any hospital authority that has a similar, sadly unfamiliar, duty Many further projects sponsored or supported by the Trust are listed under organisation and the further headings of mental health services, care of the aged, rehabilitation services, general practice, industrial health, training and education, and design and operation

BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS

VARIOUS workers, notably Dormer et al,[1] have studied the use of bronchography in pulmonary tuberculosis, but until recently the method was little applied in this condition, partly owing to the danger of extending the disease, and partly because residual unabsorbed oil obscured further radiographs Chemotherapy and the introduction of a new contrast medium, propyliodone ('Dionosil') have changed all that Except in patients with a persistently positive sputum due to drug-resistant organisms, the risk of the disease being spread after adequate chemotherapy has practically vanished, and the contrast medium disappears promptly from the lung fields, furthermore because, in the new medium, iodine is in organic combination, the rare tragedy due to iodine-sensitivity is no longer liable to occur

The routine use of bronchography in cases of pulmonary tuberculosis where surgery is contemplated has also been favoured by the increasing recognition of the limitations of the ordinary radiograph While these limitations are in some degree overcome by tomography—lateral sections are particularly helpful—the bronchi themselves can be properly delineated only by a contrast medium, and the importance of the bronchus as a factor in the physiopathology of pulmonary tuberculosis is now more fully appreciated Furthermore the tendency is to resort less often to bronchoscopy, partly because lesions in the major bronchi are known to heal readily with chemotherapy, partly because the lesser bronchi cannot be seen, but principally because bronchography is such an efficient method of "lung-mapping" that in most cases bronchoscopy is unnecessary Bronchography is less upsetting than bronchoscopy with local anæsthesia, and general anæsthesia is necessary only in young children The contrast medium itself is relatively non-irritating, although a mild febrile reaction may ensue

Most thoracic surgeons contemplating resection for pulmonary tuberculosis now routinely request pre-operative bronchography, it is of value sometimes in the investigation of "round shadows" which may be

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[1] Alexander L. Berkeley, A W, Alexander, A M. *J Amer med Ass* 1958 166, 1943

[2] The Nuffield Provincial Hospitals Trust a record of the progress of schemes and descriptions of new projects 1955–58 Issued by the Trust, Nuffield Lodge Regents Park, London, N W 1

[1] Dormer B A, Friedlander, J, Wiles F J *Amer Rev Tuberc* 1944, 50, 283, 287, *ibid* 1945, 51, 62, 455, 519

either tuberculous or malignant, as with the latter a distant "block" may be apparent, and anatomical variations from the normal bronchial pattern can be demonstrated preoperatively Merrill and Sampson,[2] analysing a series of bronchograms of their tuberculous patients in 1956 at the Highland-Alamida Hospital, Oakland, California, point out that pathological examination of resection specimens has contributed to diagnostic accuracy and that changes in the segmental bronchi are comparable with those in the major bronchi They are, however, critical of the view which accepts the mere presence of ectatic bronchi as an indication for resection, resected specimens of these bronchi are not uncommonly smooth-walled and non-caseous, which would seem to indicate that little harm would have resulted if the decision had been against operation As the effectiveness of properly managed long-term chemotherapy becomes ever more evident, the indications for operation are becoming fewer and less clear-cut The presence of distinct stenosis may indicate the need for surgical intervention, as in the "middle-lobe" syndrome or where an empyema space communicates with the bronchus But there is still a real need for accurate assessment of the results of long-term chemotherapy, and we cannot yet prognosticate clearly from the bronchographic picture regarding patients with ectatic bronchi in whom control appears to have been achieved by chemotherapy There is of course some risk of secondary infection, though it does not seem to be great, of hæmorrhage, though this is apparently unusual, and of recrudescence of disease, though this depends also on other factors such as the presence of cavities, round foci, and apical deposits, besides general factors, including inherited resistance and constancy and duration of chemotherapy

CANCER CONGRESS

SOME 2500 members and associates from more than sixty countries enrolled for the seventh International Cancer Congress, held in London this week under the presidency of Sir Stanford Cade, who read a message from the Queen, the congress patron The congress was opened on Monday by the Duke of Gloucester, and the meetings, of which we hope to give some account, were continuing until Friday

TREATMENT OF TROPICAL EOSINOPHILIA

THE syndrome of tropical eosinophilia (pulmonary eosinophilia, eosinophilic lung) is familiar to practitioners in Asia The patient is an Indian with paroxysms of coughing specially at night, added sounds on chest auscultation, significant eosinophilia, and increased shadows in the chest radiograph The cause is unknown, but arsenical treatment is usually successful Other features, which are variable, include asthma, chest pain, scanty hæmoptysis, insomnia, fatigue, weight loss, and—specially in children—enlarged lymph-glands and liver Fever is usually slight or absent, but the erythrocyte-sedimentation rate is increased The onset is typically insidious and the illness continues with remissions for weeks, months, or years—up to twenty years has been recorded[3] There are a host of causes and degrees of eosinophilia in the Tropics, but many clinicians regard tropical eosinophilia as a clear-cut entity On the other hand, Aitken and Roy,[4] in their study of 200 cases on a Bengal tea estate, found that the symptoms were protean, and the majority had no symptoms at all Gelfand[5] encountered similar cases in Rhodesia Aitken and Roy suggested that hospitals saw selected examples of a syndrome which was confined neither to the Tropics nor to the lungs, and suggested the term "eosinophilic syndrome group"

In treatment organic arsenicals, which are usually effective, may have to be given for six to eight weeks The main drawback is toxicity—especially arsenic encephalopathy, which is often fatal Such an outcome is particularly unfortunate in an illness which is not fatal in itself Danaraj[6] considers that toxic reactions are commoner than published reports would indicate He therefore studied the effects of other empirical measures, including antibiotics, sulphonamides, bismuth, cortisone, piperazine, and diethylcarbamazine Only diethylcarbamazine produced results comparable to those of arsenic Diethylcarbamazine was advocated by Friess et al,[7] who found *Wuchereria malayi* in lymph-nodes of six soldiers returning from Indo-China with tropical eosinophilia, and earlier reports of the use of this drug were favourable[8-11] In Singapore Danaraj[6] has studied the effects of diethylcarbamazine in 110 patients of whom 90% were male, over 80% adult (in other series, children and females have predominated), and over 70% Indian—although Indians form only 7 8% of the population of Singapore Selection criteria were an eosinophil-count of over 3000 per c mm, increased shadows in the radiographs, an erythrocyte-sedimentation rate of more than 10 mm in the first hour, and no evidence of past or present filarial infection Dosage was 4 mg per kg thrice daily for four days in 46 cases, and 6 mg and 10 mg per kg body-weight thrice daily for five days in 57 and 7 cases respectively The patients were observed, mostly as out-patients, for an average period of six months Symptoms improved within two to four days of treatment being started, but the response was better with the two larger dosages than with 4 mg per kg Giddiness and frequent vomiting occurred in 6 of the 7 patients given the 10 mg per kg dose, and Danaraj therefore recommends 6 mg per kg body-weight thrice daily for five days as the standard dosage Eosinophils fell to below 3000 per c mm in five to thirty days according to the initial level The chest radiograph cleared more slowly, and the erythrocyte-sedimentation rate was still increased in 25 patients at the end of the period of observation Only 1 patient—1 of 17 Chinese—showed no response 3 patients had relapses

These results are very encouraging, particularly as diethylcarbamazine is relatively non-toxic The results would have been even more convincing if a double-blind controlled trial had been carried out As the syndrome is relatively common in India and Malaya, such a trial should be readily feasible Last year Gault and Webb[12] reported finding nematode larvæ in the liver of a patient with tropical eosinophilia, but full understanding of the cause—if in fact there is a single cause—continues to elude us[13] Why is the syndrome in Malaya virtually confined to Indians? Does a genetic or dietary factor make the Indian more susceptible to a parasitic infection? Why is the cough so persistent at night? Lung biopsy at night might reveal the answer

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[2] Merrill D L, Samson, P C *ibid* 1958, 77, 561
[3] Ball, J D *Trans R Soc trop Med Hyg* 1950, 44, 237
[4] Aitken, W J, Roy, K P *ibid* 1953, 47, 419
[5] Gelfand, M *ibid* 1956, 50, 283
[6] Danaraj T J *Quart J Med* 1958, 27, 243
[7] Friess, J, Pierrou, M, Segalen, J *Bull Soc Path exot* 1953, 46, 1037
[8] Wildervanck A, Winckel, W E F, Collier, W A *Docum Med geogr trop* 1953 5 67
[9] Ganatra R D, Lewis R A *Indian J med Sci* 1955, 9, 672
[10] Chaudhuri, R N *J Indian med Ass* 1956, 27, 195
[11] Danaraj T J *Proc Alumni Ass Malaya* 1956 9 172
[12] Gault E W, Webb, J K G *Lancet*, 1957, ii, 471
[13] *ibid* p 478

Special Articles

TEN YEARS' GROWTH OF THE WORLD HEALTH ORGANISATION

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IT is interesting to recall the mood of 1945 and 1946 which led to the launching of the United Nations Organisation and some of its specialised agencies.[1] The world, reacting to the misery and disturbance of the war, was ready for, indeed expecting, concerted action to give all peoples fuller and better lives. The emergence of the atom bomb and the talk then of fearsome biological warfare also impelled a search for closer international cooperation in resolving quarrels and removing their causes. The widespread prevalence of want and disease were believed to be prominent among such causes. Hence the urgency to extend international association in functional fields as well as in those of traditional diplomacy.

As regards health, this mood simplified the acceptance of principles long advocated:

1. A single international body to coordinate health affairs.
2. Membership to be universal.
3. Functions to be comprehensive—i.e., not limited to quarantine and similar traditional functions.

Now that ten years have passed since the first World Health Assembly met in Geneva in July, 1948, examination of the application of these principles should be instructive.

Membership

During that first Assembly of the World Health Organisation, the ratifications of the constitution brought the membership of Governments to 55. Further ratifications and the accession of new countries have now increased the membership of W.H.O. to 85 members and three associate members. The only intergovernmental agencies with more comprehensive membership are the Universal Postal Union (96) and the International Telecommunications Union (91).

In 1949 and 1950 the Governments of Soviet Russia, the Ukraine Republic, Byelorussia, Bulgaria, Rumania, Albania, Czechoslovakia, Hungary, and Poland, informed the Organisation that they no longer considered themselves members of the Organisation, but, as the constitution makes no provision for withdrawal, they were regarded as "inactive". In the year ending last January the Soviet Union, Poland, Czechoslovakia, Bulgaria, Albania, and Rumania, resumed active membership.

Structure

Ten years ago there were a headquarters in the Palais des Nations at Geneva, a liaison office in the United Nations headquarters in New York, and an epidemiological quarantine office, taken over from the League of Nations, in Singapore.

Despite some initial doubts about the wisdom of its early application, the principle of regionalisation was put into effect immediately. The world was divided into six regions, and by 1951 regional organisations were operating in all. These now have headquarters as follows:

African Region	Brazzaville
Region of the Americas	Washington, D.C.
South-East Asia Region	New Delhi
Eastern Mediterranean Region	Alexandria
European Region	Copenhagen
Western Pacific Region	Manila

The Americas had long had their own regional health body in the Pan-American Sanitary Organisation, with its bureau headquarters in Washington. By an agreement of 1949 the P.A.S.B. assumed its role of the regional office of W.H.O. Each of the regional offices has grown with the years and now keeps in close contact with the health authorities of its region.

The trend of decentralisation has not stopped with the establishment of the six comprehensive regional offices, each operating with its appropriate regional committee of local Governmental representatives. A varied system of subdivisions has appeared.

In the African Region there are four areas under the supervision of public-health officers.

Even before the advent of W.H.O. the Region of the Americas had zone offices in Guatemala City and Lima. It now has six zones, each with its own headquarters.

In the South-East Asia Region there are five area representatives stationed in Burma, Ceylon, India, Indonesia, and Thailand.

The European Regional Office has not yet any geographical subdivisions. In 1956 the Eastern Mediterranean Office appointed four public-health advisers to coordinate the programmes in Libya, Saudi Arabia, and Yemen, Ethiopia, Sudan, and Somalia, Iran, Iraq, and Pakistan, and Jordan, Lebanon, and Syria. In view of the present suitability of this arrangement, a scheme for area representatives has not yet been put into force. Area representatives have, however, recently been appointed for three groups of countries, and a fourth is to be added soon in the Western Pacific Region.

Thus ten years' growth has led to a large, even complex, system of regionalisation, with subdivisions undertaking the general programme and administrative functions of the Organisation in the individual countries of the world.

A Decade of Programmes

The programmes fall into three broad groups, though in practice these have not always remained distinct.

(1) *General Technical Services*

The general technical services are given to the world as a whole. These are the traditional services which countries have found it essential to seek from an international body. They arose to meet the need for common understanding and action on the terminology and classification of the causes of mortality and morbidity, on the description of drugs and related substances, on the definition of the agents and causes of diseases, microorganisms, &c., and on the quarantine procedures acceptable for international traffic.

This traditional work has been maintained and extended by W.H.O. The International Lists of Diseases, Injuries and Causes of Death have twice been revised under its ægis. These are now being applied by many more countries in a continuing effort to produce fuller and more accurate records of both mortality and morbidity, without which health and medical programmes are liable to be aimless and wasteful. This basic statistical work has contributed much in all regions to preliminary programmes of world epidemiology. Epidemiology, in the full modern sense of the word—a study of factors influencing the health of a community—has emerged as an essential responsibility of W.H.O. Statistical data are but part of the epidemiological information needed on world and regional conditions. In such subjects as malaria, tuberculosis, poliomyelitis and the other virus diseases, "cancer", circulatory conditions, accidents, and mental disease much additional epidemiological work has been done. In most cases the prosaic but essential preliminaries have first been taken nomenclatures and classifications have been prepared, arrangements have been made for reference material, bacterial types, &c , to be distributed, and basic clinical, pathological, and therapeutic definitions have been reached Thus the way has been prepared in many countries for the application of modern measures The common understanding now being found in these basic statistical and epidemiological criteria has also meant an expansion in both the number of subjects and the geographical areas in which investigation is proceeding as a cooperative arrangement The work on malaria, bilharziasis, and enteric infections are examples of how world cooperation in research has been much helped by the agreements on nomenclature, reference material, and technical descriptions sponsored by W H O

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[1] Gear, H. S. *Brit. med. J.* 1956, ii, 471.

Another example of general action is in the health procedures for international traffic The last few years have seen significant reductions both in the prevalence of the so-called quarantinable diseases and in the oppressive and obstructive measures previously applied to shipping, aircraft, passengers, and goods in order to prevent their spread We now know more about the epidemiology of cholera, smallpox, plague, typhus, and yellow fever, and the argument that barriers are effective against them—quarantine inspection, holding of ships and aircraft, quarantining of passengers—is less often used We now believe that quarantine systems have played a relatively small part in reducing their world importance local measures taken by individual countries—e g , better water-supplies, disposal of waste products, cleaner towns and ports, and ships properly constructed and kept free from rats, &c —have been usually more effective This refreshing change in attitude has enabled the old Sanitary Conventions, so hampering to world movement, to be superseded by the much less restrictive International Sanitary Regulations of 1952[2] To resist cholera, plague, and the rest, countries increasingly depend on their own internal sanitary condition rather than on the doubtful defence of quarantine

Another action taken through W H O which has had both medical and economic advantages has concerned the international and local use of drugs, antibiotics, and the like In most countries the practitioner and the pharmacist use drugs—diagnostics, prophylactics, and therapeutics—which have been manufactured in other countries, and there is obvious need for generally intelligible and acceptable dosage standards governing potency, purity, and safety Early efforts made by the League of Nations have been carried forward, often with the assistance of W H O , and recommendations are made, for example, in the *International Pharmacopœia*[3] A list of international non-proprietary names is helping to decrease the confusion caused by the labels—often different in different countries—given to new medicinal substances It has helped manufacturers as well as doctors

The international work on biological standardisation, also initiated by the League of Nations Health Organisation, has been much accelerated by W H O By 1945, when W H O took on this work, thirty-four international biological standards—in such substances as digitalis, vitamins, antitoxins, and antisera—had been established In the past ten years another fifty have been prepared This again assists the manufacturers and distributors as well as the users of these substances The international standards are held, on behalf of W H O , in the Statens Seruminstitut, Copenhagen, and the National Institute for Medical Research, London

(2) *Education, Training, and Technical Information*

Several allied programmes may be described together in this group Governments have sought much guidance and help in the fields of medical education and technical information Indeed, in a sense, all services provided by W H O for its member countries have had, as a main objective, education and the diffusion of information

Countries eager to develop their own medical schools, and to provide themselves with the advantage of modern medicine and public health, have made use both of the W H O fellowship system (for training their own people) and of the arrangements for obtaining advice from experts who may visit them individually or in groups The fellowship programme—much indebted to earlier international schemes, including those of the Rockefeller Foundation—has been prominent among W H O activities throughout the decade

In *1947–56* 6396 fellowships were granted to people from 149 countries and territories These fellows went to 113 other countries to receive training—almost always postgraduate The subjects studied were health services by 59%, control of communicable diseases by 28%, and medical education, clinical science, and other subjects by *13%* of the fellows

The fact that W H O fellowships are now being used each year by nearly 1000 medical and allied people makes this one of the most significant postgraduate training schemes ever developed Countries are thus getting knowledge and skill to guide their own advances A large number of training institutes (universities, medical schools, research laboratories) receiving W H O fellows have become partners in the diffusion of experience and information

This movement of fellows, and the reverse flow of teachers and consultants, in so many countries and territories, must have effects beyond the specific training for which they were designed Their influence in drawing at least medical and technical communities of the world together, in creating common traditions and associations, and in giving common standards, practices, and languages, will probably continue to radiate good will and community of purpose for many years after the actual exchanges

It is too trite to claim again the value of publications in diffusing scientific and technical knowledge A whole series has been developed by W H O for its international purposes

Most originated in the League of Nations Health Organisation or in the *Office International d'Hygiene Publique* These have been issued in terms of the publication policy laid down by the Health Assembly and the Executive Board, which requires material to be selected for publication which has a direct relation to international medicine or health Thus the quarterly *W H O Bulletin*, its principal scientific journal, has included articles on laboratory studies on communicable diseases, control of disease, geographical distribution of disease, surveys of regional or world health and medical subjects, and reports of W H O field projects

Epidemiological and statistical data have been presented in monthly and annual reports to furnish essential material for research-workers and medical administrators everywhere Over thirty years of reports now make a valuable repository of world medical and health facts, incomplete and uneven in quality though the material still is The issue of summaries of national health legislation has been a routine practice for several decades, appealing mainly to certain official groups The introduction in 1952 of comparative surveys of legislation on such subjects as smallpox vaccination, nursing, leprosy, malaria, and midwives has enlarged the usefulness of the publication in question, *The International Digest of National Legislation* It has become a ready reference for medical administrators, practitioners, and others concerned in keeping the legislation of their own countries adapted to modern technical and administrative requirements

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[2] Gear H S , Deutschmann Z *Chron World Hlth Org* 1956, 10, 273

[3] Pharmacopœia Internationalis Geneva, 1951

W H O technical publications—one, the *Chronicle*, in the five official languages (Chinese, English, French, Russian, and Spanish) and others in English, French, and Spanish—help scientific and technical institutions and people throughout many countries to keep in touch with subjects of importance to international health They offer accessible guidance and reference to many medical and health groups concerned in international programmes and services So far, they have been carefully directed to be complementary to, and not in competition with, the well-known medical and health journals of international appeal published in a number of countries

(3) *Country Project Work*

This third group of activities has been the most prominent in the first ten years of W H O It became so to meet insistent demands from its member Governments for advice and help in creating new, or expanding existing, country health and medical services These requests have varied from a simple need for a visiting consultant (to advise a country for a few days on a single subject) to a complex agreement between W H O and associated international agencies to help a country over a period of years in establishing a whole health department or such a special service as tuberculosis control or a new medical teaching faculty This has been the type of service most enlarged by all international agencies in recent years It has been the main activity not only of the United Nations family of specialised agencies but also of vast programmes conducted under the aegis of the Colombo Plan, and the various bilateral arrangements sponsored by the United States of America In the case of W H O, this form of direct assistance to individual countries making requests has grown substantially In 1949 the direct expenditure on such advisory services was 2,199,456 dollars In 1957 it was 12,024,699 dollars—by far the largest item of expenditure

This form of aid to Governments is popular It is so in all W H O Regions and in all medical and health fields—clinical, preventive, and investigational Through it and the allied bilateral programmes (Colombo Plan, T C A, &c) the last ten years have witnessed the rudiments of health and medical services growing in practically all countries Modern scientific medicine, through general practitioners and hospital, through training institutions, and in many cases through special services to deal with malaria, yaws, and the like, has been extended into the most primitive communities It was to meet a fundamental principle that the advisory services given by W H O have been directed towards strengthening the local national and local services and not towards creation of new institutions and departments detached from the local political and administrative systems The aim has been to induce self-help, adjusting aid from outside to internal conditions, customs, and needs [1]

Expenditure

Expenditure is an obvious index to programme and administrative change year by year But the annual expenditure is not always a complete reflection of trends, because it is affected by such factors as changes in the value of currency, special non-recurring commitments, and emergencies

The annual financial reports of W H O reveal an uninterrupted increase in expenditure for the decade The first full programme year, 1949, showed an expenditure of 6,005,629 dollars, and the most recent, 1957, an expenditure of 17,681,877 dollars In other words, in the ten-year period the costs of the programme and administration have roughly trebled

The expenditure has been met by income from several sources, but most of these have been relatively minor Most of the regular annual income has come from the member States directly These contributions from Governments, according to an agreed scale of assessments, rose from 3,693,603 dollars in 1949 to 11,517,988 dollars in 1957

The annual expenditure in 1957 has been classified as follows

	(*Dollars*)
Organisational meetings	373,361
Operating programme	15,925,260
Administrative Services	1,383,256
Total	17,681,877

In the first year, 1948, about 66% of the assessments were collected in the year, but since 1951 the collections have been 90% in each year, and for 1957 the proportion was over 97% This is practical evidence of vigorous participation by Governments in the work of the Organisation, without which there would be uncertainty, confusion, and haphazard effort

The programmes of the Organisation have also benefited much from the contributions made by two funds the United Nations Expanded Programme of Technical Assistance for Economic Development of Under-developed Countries, and the United Nations International Children's Fund (UNICEF) In each country with a W H O project there has been counterpart expenditure to pay for the local personnel, transport, supplies, &c, necessary to complete or continue the new or improved service

Staff

The World Health Organisation took over a staff of 206 from the interim commission which had continued essential work and plans in the period between the International Health Conference 1946 and the first World Health Assembly in 1948 Many of these had previously worked in the earlier health bodies of the League of Nations, &c Ten years later, in 1958, the staff numbers 1481, distributed as follows

Headquarters and attached offices	501
Regional offices	459
Area and zones offices	38
Field staff (in projects in countries)	483
Total	1481

The staff now includes nationals of 53 of the 88 member States, and members of most branches of the medical, public-health, and nursing professions Many other members of these groups have worked for the Organisation in various ways during the decade The large number of technical meetings sponsored by W H O have drawn in temporarily from a number of countries many hundreds of clinicians, technical officers, scientists, and administrators There has been almost a constant flow of short-term consultants on behalf of W H O to assist a varied programme of projects in countries, and of plans and reports in headquarters and the regional offices Such officers are not regular staff members, but leave the health services, hospitals, and universities of their own country for temporary duty with W H O Some features of this type of arrangement have been discussed earlier [1]

General Remarks

Inheriting much goodwill, experience, and resources from previous international bodies, the World Health Organisation was designed to coordinate intergovernmental health and medical work and to cooperate with other similar international agencies both governmental and non-governmental It has proceeded far in this role Financial support has been continuous and general Participation of many interests, governmental and non-governmental, in its programmes has been keen, and the granting of resources to it has been generous Countries are using both its general world-wide technical services (epidemiological, statistical, quarantine, standardisation, drugs, &c) and its direct aid in the local development of medical and health services It has become a comprehensive organisation with a fully developed regional system. It is now a means of associating services, institutions, and individual workers in a wide variety of medical and health programmes

In terms of international arrangements, ten years is a short period, and no attempt has yet been made at detailed analysis and evaluation of the results of the work of W H O But the growing demand for the services, as shown by the growth of its expenditure, is an index of its present popularity

THE TENTH ANNIVERSARY

LAST Saturday the Minister of Health, Mr DEREK WALKER-SMITH, Q C, sent the following message to the various authorities responsible for the operation of the National Health Service in England and Wales

> Ten years ago a beginning was made with a quite new venture in the field of social welfare—the organised provision of a comprehensive health service for everybody, and today the National Health Service completes ten years' work
>
> They have been years not free from difficulty There have of course been many problems—problems of new patterns of administration, problems arising out of the nation's economic circumstances, and the multifarious problems of growth and development in new directions to meet changing needs But these ten years have been years of solid achievement, and I feel that it would be wrong to let this anniversary pass without seeking to convey to you and all engaged in the National Health Service and in the associated welfare services the sense of gratitude and appreciation so widely felt throughout the country
>
> We recognise most easily and acknowledge most readily our debt to the skill and care of doctor and dentist, pharmacist and optician, nurse and midwife, health visitor and home help, physiotherapist and radiographer, and all those many others who are in immediate contact with the individual person and his needs But there are many more whose contribution may be less apparent but is no less real I have in mind, for example, hospital domestic, kitchen, and laundry staff, maintenance workers, ambulance staff, porters, laboratory technicians, those caring for old people and for the handicapped, administrative and clerical staff, and all who, often unseen and sometimes unrecognised, by their work enable expert care to be brought more quickly and more adequately to the help of the patient
>
> I have also specially in mind the continuing and generous contribution, made not only by those whose daily work lies in the health and welfare services but by the thousands of men and women who render voluntary service of every kind It is a remarkable and encouraging feature of the past ten years that the provision of comprehensive health services by public authorities out of public funds has not resulted in any falling off in voluntary work but rather in a renewal and a resurgence of it in new and varied forms Not least remarkable and encouraging—and this is characteristic of the whole health service—has been the constant willingness of volunteers to devote their time and energies to public service as members of the authorities responsible for the local administration of the different branches of the National Health Service, thus continuing and reinforcing the tradition which has long been a distinguishing feature of administration in this country A great and often unacknowledged debt is due to authorities like your own for their work not only in promoting the public good generally, but also in ensuring that health services shall be preserved as personal services meeting the needs of individual human beings
>
> Ten years is a short period in the life of these services, and we must look ahead as well as back, deriving encouragement from the success so far won to help us in meeting the changes and chances of the future I am confident that your authority and all who are engaged in the health and welfare services will mark the tenth anniversary in this spirit, and will go forward with renewed vigour and purpose

Public Health

ARSENIURETTED HYDROGEN POISONING IN TANK CLEANERS

A T DOIG
M D St And, F R F P S, M R C P E, F R S E, D P H

ARSENIURETTED hydrogen (arsine) is an extremely toxic gas which can produce a serious illness mainly due to rapid hæmolysis Because cases of poisoning by it are comparatively rare, many doctors are unfamiliar with its action Therefore, despite the striking and rather characteristic syndrome, the diagnosis may easily be missed

I call attention here to the main features of poisoning by arseniuretted hydrogen, mention the principal occupations in which the risk is present, and describe three cases which occurred in the cleaning out of acid tanks This occupation is comparatively seldom mentioned in the literature as giving rise to cases, and is one which, though common in chemical works, is often regarded as devoid of danger

Arseniuretted hydrogen is produced whenever nascent hydrogen comes into contact with a soluble arsenical compound It was identified and described by Scheele in 1775 It is colourless, inflammable, and unstable, depositing arsenic on exposure to light and moisture. It decomposes on being heated to 230°C Its vapour density is 2 68 times that of air It is a strong reducing agent Textbooks of chemistry describe it as having an unpleasant smell like garlic, but this cannot be relied on in concentrations met with in industry, and most victims are unaware of any unusual odour

Occurrence and Incidence

Certain derivatives of arseniuretted hydrogen, such as lewisite (chlorovinyl-dichlorarsine), are used in chemical warfare Apart from the manufacture of these compounds arsine is little used in industrial processes, but its evolution from dissolved arsenical material in the presence of nascent hydrogen is used as a test for minute traces of arsenic, as in the well-known Marsh's, Fleitmann's, and Gutzeit's tests

Arsenic is a very common contaminant of metallic ores and is therefore frequently present in various commercial grades of metals, such as zinc, iron, copper, and tin It is present in iron pyrites and so finds its way into commercial sulphuric acid made from pyrites and into hydrochloric and other acids made from sulphuric acid The evolution of arseniuretted hydrogen may therefore be an accidental and undesired accompaniment of many industrial processes, and especially

NOTIFIED CASES OF ARSINE POISONING AND OF TOXIC JAUNDICE, 1945–56

Year	Arsine	All cases of toxic jaundice
1956	1	2
1955	—	—
1954	2	2
1953	—	—
1952	6 (2)	6 (2)
1951	2 (1)	3 (1)
1950	—	—
1949	2 (1)	2 (1)
1948	—	4 (1)
1947	—	—
1946	—	1
1945	—	6 (1)*

Numerals in parentheses indicate numbers of deaths

* H.M Chief Inspector of Factories in his annual Report for 1945 shows 2 deaths due to toxic jaundice in that year, but 1 of these had been previously notified in 1944

in conditions of poor ventilation may constitute an unexpected danger Arsenides are often present in furnace residues derived from metal smelting and purification, and the accidental wetting of these—e g , by rain water—has caused fatal cases of arsine poisoning

Poisoning has occurred in many industries, particularly in the smelting and refining of many metals, including gold, silver, steel, lead, zinc, tin, and aluminium, and in chemical works, as in the manufacture of acids, sulphates, and chlorides, and in galvanising, dyeing, paper manufacture, fertiliser manufacture, electroplating, and others The manufacture of a solution of zinc chloride for use as a flux in soldering, sometimes done by workmen by the rough-and-ready method of " killing " commercial hydrochloric acid with a piece of scrap zinc, may give rise to dangerous amounts of arseniuretted hydrogen Several professional chemists have been affected in the course of their laboratory work Dimethylarsine is well known as having been the cause of many fatal cases of poisoning in residents of damp houses, it was liberated from Scheele's green, a wallpaper pigment no longer used as such in this country, by the action of a mould

It seems likely that most cases which are recognised are notified to the Factory Inspectorate, because, apart from certain research departments and laboratories not under the Factories Acts, exposure to arsine would most often take place on factory premises Cases are usually notified either as " toxic jaundice " or as gassing accidents, but they could conceivably be notified as toxic anæmia or even as arsenical poisoning During the twelve years 1945–56 13 cases, 4 of them fatal, of poisoning by arseniuretted hydrogen came to the notice of the British Factory Department (H M Chief Inspector of Factories 1945–56) The accompanying table shows the distribution by years and, for comparison, the total number of notified cases of toxic jaundice due to all causes, including arseniuretted hydrogen

This table brings out the important role of arseniuretted hydrogen in causing toxic jaundice in peacetime, because if we exclude 1945 (when all 6 cases were due to trinitrotoluene), 13 of 20 cases were due to arseniuretted hydrogen in 1946–56, and 13 out of 15 cases in 1949–56 The causes of the 26 cases of toxic jaundice were as follows

Arseniuretted hydrogen	13 (4)
Trinitrotoluene	6 (1)
Carbon tetrachloride	2
Chlorinated naphthalene	1
Paint-remover	1 (1)
Other	3

Numerals in parentheses indicate numbers of deaths

The occupations of the 13 persons who were poisoned by arseniuretted hydrogen were as follows

Tin smelting, handling arsenical dross	6 (2)
Cleaning sulphuric acid tanks	3 (1)
Laboratory workers	2
Cleaning reaction in vessel which had contained arsenic acid	1(1)
Mixing oxalic acid and other chemicals in vessel contaminated with As O,	1

Numerals in parentheses indicate numbers of deaths

The 13 cases occurred in seven incidents, all 6 tin-smelters being affected in one and both laboratory workers in another An excellent account of the 6 cases in the tin-smelters is given by Macaulay and Stanley (1956)

Symptoms and Diagnosis

Arseniuretted hydrogen is one of the most toxic gases known Concentrations of 3–10 p p m will produce slight symptoms after several hours' exposure, and concentrations of 16–30 p p m are dangerous after $^1/_2$–1 hour The maximum allowable concentration recommended by the International Labour Office for an 8-hour working day and the " threshold limit value " adopted by the American Conference of Governmental Industrial Hygienists, 1957, are 0 05 p p m (compared, for example, with 100 p p m for carbon monoxide) Repeated exposure to low concentrations may have a cumulative effect

Two simple chemical tests are available for detecting small concentrations of arseniuretted hydrogen, one using silver-nitrate papers and the other mercuric-chloride papers The Department of Scientific and Industrial Research (1940) describes a quantitative test

After exposure to toxic concentrations of arseniuretted hydrogen there is usually a delay of 2–24 hours before the onset of symptoms When arseniuretted hydrogen enters the blood-stream it combines with the hæmoglobin and hæmolyses the red blood-cells The first symptoms are usually vague malaise, nausea, giddiness, and headache, rapidly progressing to severe illness with vomiting, intense headache, pains in the loins, and the passage of dark urine (hæmoglobinuria) The progress of hæmolysis rapidly causes profound anæmia The liver and kidney functions are severely disturbed and usually break down in the effort to eliminate the products of the disintegrated corpuscles Jaundice is usually evident on the 2nd or 3rd day and increases to an intense coppery hue There is oliguria with albumin, casts, hæmoglobin, and methæmoglobin, and in severe cases there is suppression of urine Œdema of the lungs, with accompanying cyanosis, is a common complication, and in fatal cases there is usually delirium followed by coma

It will be appreciated from this description and the three illustrative case-reports below that a sudden onset of severe illness with gastric upset and the passage of urine the colour of port-wine in an industrial worker or chemist is sufficient to direct suspicion to the possibility of poisoning by arseniuretted hydrogen Rapidly developing jaundice, anæmia, and evidence of kidney damage greatly strengthen the suspicion Inquiry should be made about the patient's occupation, particularly the precise work on which he was engaged during the previous 24 or 36 hours The whole working-time should be accounted for because exposure may have been limited to a few minutes The diagnosis is clinched by obtaining a history of exposure or by finding arsenic in the urine, because during the acute stage and for some weeks afterwards arsenic is excreted by the kidneys

In making a retrospective diagnosis after recovery in patients where the correct ætiology was missed during the acute stage, examination of the hair and nails may reveal arsenic In this connection the method of activation analysis of tissues described by Dewar and Lenihan (1956) deserves mention This very sensitive method depends on the induction and subsequent measurement of radioactivity in the sample by treatment in a nuclear reactor It enables very small amounts of tissue to be analysed, and abnormal amounts of arsenic may be found in a single hair

Prognosis and Treatment

Prognosis turns largely on the state of the kidneys and is generally related to the amount of urine passed the smaller the amount the graver is the case Death usually takes place between the 4th and 10th days Kober and Hayhurst (1924) give the fatality-rate of recorded cases as 25–30% They suggest that this may be artificially high because fatal cases tend to be recorded more than recoveries Locket et al (1952) cite mortality-rates of 20–31% Hunter (1955) refers to 7 deaths in 25 cases (28%) in tin-refining In the 13 cases referred to above it is 31%

The danger being usually intermittent and fortuitous, the patient is rarely actually exposed to the gas when symptoms develop If he becomes ill while at work he must immediately be withdrawn from exposure, and any contaminated clothing must be removed Early removal of the patient to hospital is essential, and general measures should be instituted forthwith to deal with pain and anxiety and to minimise shock Early deaths are often due to pulmonary œdema When this is present, oxygen, preferably under pressure, probably offers most hope of averting death

High hopes that dimercaprol would prove of value have not been sustained, it has been used in most of the recently published cases, but the results have been far from convincing, even when the dosage was adequate Locket et al (1952) say that, although it is of doubtful value, dimercaprol should be given if the patient is seen within the first 24 hours, after that it is more likely to add to his burden

Dextrose and saline solution given intravenously with calcium gluconate has been advocated, but the daily fluid intake must be kept low in anuria and severe oliguria and the volume and composition of the body fluids as nearly normal as possible Hyperpotassæmia must be guarded against

Most workers advocate transfusion, preferably with packed cells, but Locket et al say a transfusion should only be given if there is severe anæmia McKinstry and Hickes (1957) say that if they see a patient with symptoms of severe poisoning, they intend to begin massive exchange transfusion as soon as the diagnosis is made, thereby helping to reduce the amount of arsenic and arsenical compounds in the blood and to get rid of reduced hæmoglobin and cellular debris and so to lessen or to prevent the blockage of the renal tubules

Cases in Tank Cleaners

The three cases briefly described here occurred at different times in different chemical works, but all were in men who had entered tanks, which had contained sulphuric acid, to clean them All the tanks had held acid made from iron pyrites—in two cases exclusively, in the third, a tank used for transport of acid by rail, oleum (fuming sulphuric acid), made by burning sulphur, had also been carried occasionally

The arsenic content of sulphuric acid made from pyrites varies a good deal but, calculated as As_2O_3, is usually about 0 2–0 3% and may sometimes be more Glaister (1908) cites arsenic contents of commercial sulphuric acid up to 0 15% and for hydrochloric acid as much as 0 691% Since the tanks were lined with lead, it was expected that the deposit would be almost entirely composed of lead sulphate Analysis of part of the deposit concerned in case 2 below, however, showed that it contained 45 0% by weight of As_2O_3, and a later sample from another tank contained 18 6% It seems that the arsenic impurities in sulphuric acid tend to settle out on standing Glaister (1908) quotes Cameron as having reported in 1856 that about 1 oz of crystallised arsenious acid was deposited after long standing from 8 lb of sulphuric acid

When the deposit is not very hard it can be removed by directing a strong jet of water on to it from outside the tank When it is hard, the tank has to be entered and the deposit removed by hand with such tools as a scraper and a shovel Cleaning may be required at intervals of 6–12 months, and the method of hosing, followed if necessary by entry, has been used for years Chemists, managers, and workmen do not appear to have anticipated the presence of any dangerous gas, and no special precautions, such as the use of breathing-apparatus, have in the past been taken in the three factories concerned Suitable protective clothing was, of course, provided and worn According to the size of the tank whether it contained internal baffle plates or not, the hardness of the deposit, and other factors, the cleaning of one tank might take a few hours or a few days

Case 1—A man, aged 52, was certified as having died of hæmolytic anæmia Death was not definitely attributed to occupation, and no suggestion was made that arsine might have been the cause The occurrence came to my notice several months after death, and on inquiry the typical story of poisoning due to arseniuretted hydrogen came to light

Exposure and onset—The man had been employed for some years at a factory where sulphuric acid was manufactured from iron pyrites by the chamber process On a Saturday morning he entered a stock tank, which had contained concentrated sulphuric acid, to clean it He was in the tank for about half a hour, from 8 30 to 9 A M He finished his shift as usual at noon and went home He became ill about 5 30 P M on that day with colic, abdominal pain, and vomiting Next day he was admitted to hospital, where he died on the 6th day of the illness

On admission he was much jaundiced and anuric 2 oz of urine the colour of port-wine was obtained on each of the following 2 days, and thereafter he was anuric until death His urine contained hæmoglobin and methæmoglobin His blood hæmoglobin was 81% on admission but on the day preceding death had decreased to 45% and the red cells to 2,760,000 per c mm No hæmolysins were found in his blood Treatment was by intravenous drip with glucose

Necropsy findings—The lungs showed severe hæmorrhagic œdema, with many hæmosiderin-laden phagocytes in the alveoli The liver was slightly enlarged, rather pale, and soft, but without fatty degeneration or necrosis, the centres of its lobules showed a good deal of pyknosis of the liver-cells The kidneys showed severe hæmoglobinuric nephrosis, almost all the collecting tubules containing precipitated hæmoglobin or acid hæmatin The loops of Henle and the distal convoluted tubules contained many casts The glomeruli were practically normal The cause of death was acute hæmolytic anæmia and renal failure

Case 2—A man, aged 34, had been a chemical-works labourer for more than 5 years and had cleaned many acid tanks in that time Before his illness he and his usual mate had been engaged in cleaning a rail-car tank which had been used for many years for transporting sulphuric acid It was 15 ft long by 5 ft in diameter, and had one man-hole, the interior was divided into three compartments by two baffle-plates, each with a man-hole The tank had usually carried concentrated pyrites acid but in recent months had contained oleum at times The deposit was very hard and could not be dislodged after flooding and hosing The men took it in turns to enter the tank for spells of about ½ hour each. On the Friday, when work started, and on the following Monday each man probably spent 2–2½ hours inside the tank, on the Saturday morning about 1 hour each, and on the Tuesday about 1½ hours each before noon, when the work was completed. About 2½ tons of deposit was removed. The mate was unaffected, but the patient became ill early on Tuesday evening with nausea, abdominal pain, and headache, which later became severe and were accompanied by vomiting.

On admission to hospital next morning he had hæmoglobinuria and was icteric. Examination of his blood showed hæmoglobin 80%, red cells 4,400,000 per c.mm., and white cells 14,000 per c.mm. Serological tests for Weil's disease were negative. The man made an excellent recovery without any specific treatment, and no transfusions were required.

Laboratory tests.—Analysis of two types of pyrites acid which had been carried in this tank car showed an arsenic content, expressed as total As, of 0.27% and 0.36%. The arsenic content of a sample of oleum was 0.01%. The men had used a steel scraper, an iron shovel, and a galvanised iron bucket in the tank. Laboratory tests with the deposit showed that arseniuretted hydrogen was generated from it by using zinc, and traces by using mild steel. A quantitative analysis of part of the deposit removed last during cleaning showed the astonishing figure of 45.0% arsenic calculated as As_2O_3.

Case 3.—A man, aged 35, was notified as having toxic jaundice of unknown origin, the notification being received after his recovery. Though it was suspected that his illness might have had an occupational cause, the possibility that this might be arseniuretted hydrogen had not been considered, and the mangement and staff of the factory were unaware that this hazard existed in the works.

Exposure and onset.—On the day his illness started, the patient had entered an acid-storage tank to clean it. The tank measured 6 ft. high by 9 ft. in diameter and had held concentrated oil of vitriol (98% sulphuric acid) *made from pyrites.* After washing out the tank several times with a hose he had entered it, taking a copper shovel and a galvanised pail with him. He spent two or three periods of ½ hour each in the tank. When he returned home in the evening he felt tired and was unusually thirsty but had no appetite. Severe headache developed, and during the night he vomited and passed urine which he described as nearly black.

On admission to hospital next day he was extremely ill and jaundiced, and his urine contained methæmoglobin and albumin. Liver-function tests showed some liver damage.

Treatment and progress.—He was treated with intravenous methylene-blue and ascorbic acid and with cortisone 200 mg. daily during the acute stage. In addition he had a high-carbohydrate low-fat diet. He made a full recovery. His hæmoglobin decreased to 40%, but at the time of discharge was 95%. Normal liver and kidney functions were entirely regained, and 2 weeks after his discharge his serum-bilirubin was 0.4 mg. per 100 ml., his hæmoglobin was 100%, his urine was normal except for excess urobilinogen, and he looked and felt well.

Laboratory tests.—Specimens of his hair and nails were obtained 10 weeks after the onset and subjected to analysis for arsenic content by the activation technique. The specimen of hair was reported as containing 7.6 p.p.m. of arsenic and the nails 4 p.p.m., both values being rather high. The tests, repeated after 4 months, showed the arsenic content of the hair as 1.5 p.p.m., which is within normal limits, but the content of the nails was still rather high at 6 p.p.m.

Prevention

Undoubtedly the most important factor in prevention is a knowledge of the risk. The three cases described occurred because the danger was not appreciated, and it seems incomprehensible that the managements of the three factories did not foresee the risk of generation of arseniuretted hydrogen during the work of cleaning the tanks. The cases occurred in 1949, 1951, and 1956, and obviously there had been little or no interchange of information between the factories nor effective publication in the chemical trade journals, and the references to the cases in the annual reports of H.M. Chief Inspector of Factories had been missed. It is to be hoped that a knowledge of this serious danger will soon permeate to the staffs of all factories where acid tanks may have to be cleaned, and from them to the workmen who have to do the job.

So far as possible, acid tanks should be cleaned without entry. When the deposit is soft, this can usually be done by repeatedly flushing with water and draining. When the deposit is hard, softening might be effected by strong alkalis or by steam. According to the nature and construction of the tank, in some cases it might be possible to bore or cut a hole or holes in the bottom or sides to allow of the insertion and manipulation of scraping tools. When the tanks are entirely composed of sheet lead, this would not offer much difficulty. It might be possible to prevent the deposit from becoming very hard by arranging for regular cleaning at relatively short intervals.

Proper equipment for the job should include protective clothing consisting of acid-resisting suits, head covering, and rubber boots and gloves, and non-metallic tools, such as scrapers, shovels, and buckets. Breathing-apparatus should be worn if entry is necessary, the most convenient type probably being an air-line mask enabling the worker to breathe fresh air through a flexible hose extending to the open air outside the tank. A mate should always be immediately at hand outside, and, where the entrance to the tank is small, or where there are interior baffle-plates which might hamper rescue in an emergency, it is probably wise for the worker entering to wear a safety belt, the attached rope being held by his mate outside.

Legal requirements are quite definite about precautions which have to be taken when work is done inside enclosed spaces where dangerous fumes are liable to be present. They are laid down in section 27 of the Factories Act, 1937, modified by section 11(2) of the Act of 1948. In factories to which the Chemical Works Regulations, 1922, apply Regulations 6–9 are particularly relevant to the work in question and must be observed.

Discussion

Poisoning by arseniuretted hydrogen produces a serious illness with a striking clinical picture. The dominant features are acute hæmolysis and jaundice, and perfectly correct diagnoses, such as acute hæmolytic anæmia, hæmolytic jaundice, and toxic jaundice, are easily made on the clinical findings. The true ætiology, however, is often overlooked. In two of the three cases described (cases 1 and 3) the possibility that arseniuretted hydrogen might be the cause does not appear to have been considered until investigations were made some time after the illnesses, although certainly in case 3 an industrial cause was suspected. Case 2 was correctly diagnosed by the general practitioner as arsine poisoning; he had, by an extraordinary coincidence, attended case 1 about 18 months previously and instantly recognised the typical syndrome.

The reason why the ætiology is missed is of course the rarity of the condition. Very few physicians in general or in hospital practice ever have an opportunity of seeing a case. It should, however, be noted that arseniuretted hydrogen is one of the commonest causes of industrial toxic jaundice in peacetime, when trinitrotoluene is not being manufactured on a large scale

The ignorance of chemists and plant managers about this grave risk seems to me much more remarkable It is a well-known fact that acid made from pyrites contains arsenic as an impurity, and the presence of arsenical compounds in the deposit in tanks which have contained commercial sulphuric or hydrochloric acids should be appreciated and the danger of evolution of arsine recognised In none of the three factories concerned with these cases was entry into acid tanks for cleaning considered to carry any risk of exposure to dangerous gases, and such entry had taken place on several occasions without special precautions having been taken So far as is known, no harmful effects had followed these previous entries Even after the occurrence of cases 1 and 3 the managements and technical staffs were unable to pinpoint the hazard At the factory where case 2 occurred, however, the origin of the gas was recognised when the correct diagnosis of poisoning by arseniuretted hydrogen was known, and the works chemist demonstrated its evolution from the deposit from the tank with iron and zinc, the metals of the shovel and galvanised bucket used

It is quite probable that unrecognised cases of arsine poisoning have occurred in the past from the cleaning of acid tanks when less thought was given to possible occupational causes of illness than today The extreme toxicity of the gas makes it essential that works managers, chemists, and foremen in factories where sulphuric acid is stored in tanks should show a much greater awareness of this grave danger than they have shown in the past

It seems too that a reminder to the medical profession would not be out of place, for, although poisoning with the gas usually produces a very characteristic syndrome, it is one which few physicians have an opportunity of seeing, and the diagnosis, or at least the ætiology, is thus easily missed

It is worth emphasising too that H M Factory Inspector should be notified immediately the cause of the illness is ascertained or, even better, as soon as an industrial cause is suspected If this were done, an immediate investigation would be made at the factory Since the cleaning of one tank may take several days, as in case 2, early notification—for example by telephone—of one case may lead to the institution of suitable preventive measures before a second case results H M Medical Inspectors of Factories will be ready to give assistance in regard to diagnosis and investigation

Summary

Poisoning by arseniuretted hydrogen, though relatively rare, is one of the commonest causes of toxic jaundice in peacetime In spite of the typical syndrome cases may be missed

The risk of poisoning by arseniuretted hydrogen in cleaning tanks which have been used for storing or transporting strong acids does not appear to be fully appreciated Three cases arising from cleaning sulphuric-acid tanks are described, one of them fatal

This danger should be made widely known among technical staff of factories where strong acids are stored Doctors and factory managers should realise the importance of early notification of cases to the Factory Inspectorate

I received a great deal of help and information from managers, chemists, and other staff of the factories where the three cases occurred and from general and hospital practitioners who attended the affected men I thank them all, and Dr Colin Campbell for information about the necropsy findings in case 1, and Dr J M A Lenihan for the activation analyses on material from case 3

REFERENCES

Department of Scientific and Industrial Research (1940) Arsine London
Dewar, W A, Lenihan, J M A (1956) *Scot med J* 1, 236
Glaister, J (1908) Poisoning by Arseniuretted Hydrogen or Hydrogen Arseníde Edinburgh
H M Chief Inspector of Factories (1945–56) Annual Reports London
Hunter, D (1955) The Diseases of Occupations London
Kober, G M, Hayhurst, E R (1924) Industrial Health Philadelphia
Locket, S, Grieve, W S M, Phillips, L (1952) *Trans Ass industr med Offrs*, 2, 14
Macaulay, D B, Stanley, D A (1956) *Brit J industr Med* 13, 217
McKinstry, W J, Hickes, J M (1957) *Arch industr Hlth*, 16, 32

Infectious Diseases in England and Wales

Disease	Week ended June			
	7	14	21	28*
Diphtheria	2	—	—	5
Dysentery	883	893	839	873
Encephalitis				
Infective	3	4	2	2
Post-infectious	1	10	1	1
Food-poisoning	184	275	279	261
Measles, excluding rubella	6433	5594	6109	6026
Meningococcal infection	20	15	16	22
Ophthalmia neonatorum	40	29	14	27
Paratyphoid fever	6	2	1	8
Pneumonia, primary or influenzal	265	247	214	218
Poliomyelitis				
Paralytic	16	20	22	29
Non-paralytic	15	9	14	14
Puerperal pyrexia	203	200	223	170
Scarlet fever	615	666	659	662
Smallpox	—	—	—	—
Tuberculosis				
Respiratory	571	560	555	565
Meninges and C N S	8	5	8	7
Other	90	104	91	80
Typhoid fever	7	8	4	1
Whooping-cough	641	747	800	783

* Not including late returns

Points of View

EVOLUTION AND ILLNESS*

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> " What do these rudiments, these apparent imperfections mean? There must be some cause for them, they must be the necessary results of some great natural law "—A R WALLACE (1855)
>
> " It is a relief to have some feasible explanation of the various facts, which can be given up as soon as any better hypothesis is found "—CHARLES DARWIN to A R WALLACE (1868)

A FRESH field of clinical investigation opened when it was recognised that certain primary disturbances of the human mind can damage *distant and diverse* structures throughout the body Doctors working within the complex environment of modern society are re-examining some aspects of disease that they believe to be related to such factors as the growing complexity of life and the closer impact of parents on their smaller families There is a desire to contain the vagaries of stress-conditioned illness within the bounds of a rational physiology, and an increasing recognition that the *anatomical* distribution of the consequent organ damage is often influenced by the genetic constitution of the patient, of his family, and of his race

In the wild state of Nature, we understand something of the basic laws of selection acting on gene-conditioned variations in plants and animals In agricultural and horticultural selection we see at work the minds of men, seeking to improve their stock by the conscious application of skilled experience In man, since he became human, unique forces, still largely veiled in mystery, have acted to condition his fitness for selection, and to produce, partly by the greater relative safety of a civilised environment, certain modifications of behaviour and of structure Yet all this great advance has been achieved with the maintenance of—and (some believe) partly because of—the very generalised human anatomical form Man reveals an "astonishing conservatism of anatomical structures as the result of which their traces may still be detected millions of years after they have ceased to have any function" (Le Gros Clark 1950)

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* The text of the essay from which this article has been condensed can be obtained from the author

Commonly found on human skin are structures which, judging by their anatomy and histology, are significant ancestral characters dating to man's early mammalian and amphibian-reptilian evolution In the past a study of these structures, which were regarded merely as "beauty-spots" or "birthmarks", would have seemed irrelevant to clinical medicine But their identification as evolutionary vestiges (de Cholnoky 1939, Laidlaw and Murray 1933, Stout 1948) adds a new interest to the study of the supernumerary nipple and the pigmented moles and other nævi, especially since workers in human genetics (McKusick 1956) have demonstrated, in such diseases as the Marfan syndrome, a close genetic linkage between superficially trivial anatomical characters and grave hereditary diseases

OBSOLETE DEFENCE MECHANISMS

The suggestion that obsolete defence mechanisms from very remote dates in human evolution can be reactivated under the influence of emotional stress or long-continued anxiety (Harper 1953) seems less improbable in the light both of the clinical facts and of the collateral evidence deriving from the influence of pædomorphism in the recent development of the human brain This concept—that in certain highly progressive species, including man, evolutionary advance has been achieved by retention in the adult organism of structures formerly found only in the fœtal stages of the species—was first given the name of "pædomorphosis" by Garstang (1922) Hardy (1954) emphasises the close identity of Garstang's theory with Bolk's (1926) thesis of "fœtalisation" especially of the human skin de Beer (1951) wrote "It must not be pretended, of course, that pædomorphosis itself can account for the essential character of man—his mental capacities, we may, however, say these could not have been evolved without pædomorphosis" The clinician who appreciates the profound anatomical significance of a pædomorphic element in modern human evolution may properly inquire into the possible impact of such a phenomenon on the physiology and diseases of contemporary man Should it prove true that anatomical characters of fœtal type have been significantly retained in the human adult, a hypothesis that certain illnesses are based upon "morbid echoes" of archaic defence reflex patterns deserves careful examination

In relating human illness to reflex defence patterns, three groups of possible physiological mechanisms might be considered

Group 1—Those reflex patterns that are present and are still used for their physiological purpose in man Under certain adverse conditions of the environment, I suggest, a close association may exist between the reflex defence mechanism and a grave pathological process In this connection I shall refer with frank but necessary oversimplification, to the ætiology of phlebothrombosis

Group 2—Here no physiological service is immediately obvious at human level, but the clinical course of certain diseases suggests that they may be associated with obsolete reflex defence patterns of vital importance in the mammalian forebears of man Peptic ulcer can be an illustration here

Group 3—These reflex patterns are so archaic that it might seem absurd to suggest that human illness could be related to them Yet I believe that this will be shown to be true Proof of the existence on human skin of common structures relating man to the amphibian-reptilian era of his evolution will encourage the further investigation of what may prove to be an important new aspect of disease As illustrations, I shall mention, with diagrammatic oversimplification, three illnesses allergy, diabetes, and certain neoplastic states

Group 1

Every physician who has practised in the wards of hospitals where acute cases are nursed must have been puzzled by the frequency with which excellent work meets the unexpected and often grave complication of pulmonary embolism, due to detachment of a clot which has formed in the veins In relation to my hypothesis, the significance of this group of illnesses lies in the laboratory evidence that, in the lower mammalia and in man, blood tends to coagulate more quickly when danger threatens Stoker (1945, 1952) has demonstrated a considerable reduction in the clotting-time of rabbits after an incident causing them fear A similar reaction has been demonstrated by him in human beings under emotional stress Hunter et al (1941), in 351 unselected consecutive necropsies, examined the calf muscles macroscopically and microscopically and found antemortem clots (often bilateral) in rather over half of them

Deferring to most contemporary opinion, the clinician, losing his patient from massive pulmonary embolism consequent on phlebothrombosis, attributes the tragedy to rest in bed, to a fall in blood-pressure, or to debility. But observation over many years has convinced me that fear, or lack of confidence by the sensitive patient, has sometimes played a significant part Doctors, nurses, and administrators should be taught these physiological and clinical possibilities and recognise their implications Though nervous patients often find security in the wards of a hospital, and are relieved of some of the morbid potential of their anxiety in this environment, others react unfavourably to the often little-concealed events of the general ward It may well be that some of the cases of phlebothrombosis attributed to the uncomfortable seats in air-raid shelters were associated with this shortening of the clotting-time in the presence of fear

Here, then, is one example of an illness whose precipitating cause may be the morbid echo of a physiological process This particular process, we may suppose, was originally evolved, perfected, and selected because it prevented blood-loss in battle or in flight and so conserved the integrity of the blood-volume for escape or victory

Group 2

Harvey Cushing (1932) drew attention to the enormous literature, the vast number of theories, and the conflicting evidence surrounding the local lesion in peptic ulceration He expressed his opinion that, whatever the exact mechanism causing the local lesion might be, it was in the nervous system of man that the true causation of this illness would be discovered It is increasingly accepted that in the modern prefrontal areas of the human brain are centres closely linked with the age-old autonomic system. Brandt (1922) suggested that the parasympathetic antedates all other nervous structures in phylogeny, except the very early endocrine system Should pædomorphosis be proved to have conditioned man's recent evolution, apparent inconsistencies may be better understood, and the possibility that this type of illness may be based upon an obsolete physiology may be established as a fact In a feeding animal faced with an emergency in which a maximal supply of blood to the skeletal muscular system was required, we may discern a reflex mechanism that, by violent closure of the pylorus and the act of vomiting, halted digestion When fear and anxiety produce a morbid dynamic of tension in the human brain, some echo of this reflex may, I believe, be producing the organ dysfunction and damage

Group 3

Let us now briefly examine the distant end of the time scale, the amphibian-reptilian epoch of human evolution Elsewhere I have described manifestations of allergy as possibly based on the integrated oxygenating reflexes of skin, lungs, and gills—a normal physiological mechanism in the distant amphibian era (Harper 1948, 1951, 1953, 1955) I believe it is but the logical application of a true hypothesis to seek for other illnesses in this third group of reflex defence patterns, in view of the unique, yet very common, reptilian structures demonstrated on human skin by Laidlaw and Murray (1933) in their classical work on pigmented moles and their relationship to the evolution of the hair follicles in man

Long before the discovery of insulin, Osler (1892) wrote of diabetes mellitus "Mental shock, severe nervous strain, and worry precede many cases" Twenty-five years' experience in directing a diabetic clinic have convinced me that this mysterious and highly complex illness will be recognised, in some of its forms, as a disease of stress It is perhaps significant that the islet tissue of the pancreas retains its own autonomic nerve-supply, that to the beta cells being especially heavily innervated by the age-old parasympathetic system, so closely connected in the distant past with archaic reflex patterns of defence

Is it possible that the future may reveal knowledge that will justify another unexpected, yet I suggest logical, extension of the hypothesis, and bring within its scope as "morbid echoes" of this third group of reflexes certain types of malignant cell-growth? Remarkable regeneration of entire limbs after damage was a commonplace event in the amphibian-reptilian epoch of man's evolution The nature of the physiological forces at work in the organism while such extensive injury was being repaired is still unknown The process of such massive yet orderly repair can still be watched in the axolotl, that remarkable example of neoteny (extension of the larval stage), where mature reproduction occurs in the larval form of the amphibian *Amblystoma tigrinum* We cannot at present comprehend these physiological mechanisms even in such lowly organisms I believe, however, that in the reactions of man's body to certain exogenous and endogenous carcinogenic stimuli we may yet find that we are witnessing the results of a distorted and destructive physiology of archaic origin that formerly furthered active yet purposeful cell-growth after injury The influence of anxiety and mental shock on the course of a malignant illness has become increasingly apparent to clinicians (Ogilvie 1957)

CONCLUSION

The theory of evolution has become one of the great cosmic generalisations, and in whatsoever sphere it has been wisely applied it has enlightened what before had been an ill-defined field of human experience The time is ripe for its logical and bold application to clinical medicine

REFERENCES

Bolk, L (1926) Das Problem der Menschwerdung Jena
Brandt, W (1922) *Z Anat EntwGesch* 65, 284
Clark, W E Le G (1950) History of the Primates, p 7 London
Cushing, H (1932) *Surg Gynec Obstet* 55, 1
de Beer, G R (1951) Embryos and Ancestors London
de Cholnoky, T (1939) *Arch Surg* 39, 926
Garstang, W (1922) *J Linn Soc* (Zool) 35, 81
Hardy, A C (1954) in Evolution as a Process (edited by Huxley, Hardy, and Ford), p 122 London
Harper, R M J (1948) *Lancet*, i, 899
— (1951) *ibid* ii, 1134
— (1953) *Brit med J* i, 392
— (1955) *Practitioner*, 174, 193
Hunter, W C , Sneeden, V D , Robertson, T D , Snyder, G A C (1941) *Arch intern Med* 68, 1
Laidlaw, G F , Murray, M R (1933) *Amer J Path* 9, 827
McKusick, V A (1956) Heritable Disorders of Connective Tissue St. Louis.
Ogilvie H (1957) *Lancet*, ii, 35
Osler, W (1892) Principles and Practice of Medicine, p 295 Edinburgh and London
Stoker, S B (1945) *J sci Instrum* 22, 146
— (1952) *Lancet* ii, 709
Stout, A P (1948) Biology of Melanomas, p 38 New York
Wallace, A R (1855) *Ann Mag nat Hist* 16, 184

Congresses

GYNÆCOLOGY AND OBSTETRICS

At the second world congress of the International Federation of Gynæcology and Obstetrics, held in Montreal on June 22–28, 61 nations were represented

Canada's Problems

Mr **Waldo J Monteith**, Canadian Minister of National Health and Welfare, remarked that Canada is the third largest country in the world, occupying $3^{1}/_{2}$ million square miles, with a small population of 17 million largely based on a 200-mile strip across the country's southern border There is disparity of progress because Canada has been settled in waves, first Quebec, then Ontario, and the west some hundred years later, only now is the north being settled

Disordered Uterine Activity

Professor **Beloshapko** (U S S R) said that the idea of regulating the character of labour was generally accepted, and he drew attention to the vagaries of uterine action mentioning precipitate labour and inertia Inertia he believed to be the more important Having stated that the aim in uterine inertia was to reduce the necessity for operative procedures, he described many methods of stimulating uterine contractions In his summary of prophylaxis and treatment he stressed psychoprophylaxis, exercises, massage, and ultraviolet radiation, and the correction of sleeplessness by having special sleeping-rooms and by the careful organisation of the leisure especially of long-stay patients He believes in adequate feeding and in not putting the woman to bed too soon in her labour

The Hypothalamus

Prof G W **Harris** (Britain) described very clearly the careful experiments by which the relationships between hypothalamus, pituitary, reproductive organs, and breasts were established Impulses from the hypothalamus reach the anterior lobe of the pituitary gland by way of the vascular portal system, as has been shown by transplanting the pituitary gland first into the capsule of the kidney, when its hormone activity ceased, and then returning it to its original site, where the portal circulation was reestablished and pituitary function restored Not only has the hypothalamus a depressant action on the adenohypophysis but also there is a stimulating action Follicle-stimulating hormone may be released under the stimulation of tumour, and Professor Harris suggested that precocious puberty resulting from hypothalamic lesions may be explained in this way

The humoral interplay between hypothalamus and adenohypophysis is clearly established by the absence of any effect if the pituitary is stimulated electrically, in contrast to the marked effect if the hypothalamus is given a similar stimulation

The relationship between hypothalamus and neurohypophysis is by contrast a nervous one Stimulation of the hypothalamus leads to the production by the neurohypophysis of oxytocin, which in turn causes pregnant uterine muscles to contract and also causes the ejaculation of milk from the breast by its action on the contractile tissue in the mammary gland

The precise routes by which afferent stimuli reach the hypothalamus are not clear, probably because they are so varied This whole study accords with the known effect of emotional and other environmental stimuli on both uterine action in labour and successful lactation It may now be said that the precise way in which fear and other harmful stimuli affect parturition and lactation is well on the way to being worked out

Amniotic Membrane

Professor **BAUTZMANN** (Germany) gave a fascinating account of the muscular activity of the amniotic wall in the chick embryo and compared this with the absence of any corresponding muscular activity in higher mammals He expressed the opinion that the rhythmic activity of the amniotic membrane, which was illustrated by film, had the important effect of moving the nutrient material around the chick, and he showed conclusively that this movement was independent of fœtal activity

Fertilised Ovum

Dr **BRADLEY PATTEN** (U S A) said that the fertilised ovum develops a thick wall around it, and this has two purposes (1) it acts as a barrier to the entry of other spermatozoa, and (2) it prevents the enlargement of the fertilised egg during the early days of division and subdivision and so keeps it small enough to pass through the fallopian tube Apparently, too, this cluster of cells with its thick envelope is particularly sticky opposite the inner cell mass and this facilitates implantation Dr Patten described and illustrated the development of the fœtal circulation He showed how the primitive tubular heart begins to contract before any connection has been made with the primitive blood-vessels, and illustrated the early formation of blood-cells and the coalescing of primitive blood-vessels

Sex Chromatin

Prof **MURRAY L BARR** (Canada) spoke briefly about the three methods of examination for female sex chromatin—by mucosal smear, skin biopsy, and blood film He drew attention to the occasional flattening out of the chromocentre as a source of error The two main groups of disordered sexual development comprise those exhibiting partial masculinisation and those exhibiting intersex

It is important to distinguish the adrenogenital syndrome from male pseudohermaphroditism so that cortisone may be started without delay and the severe metabolic crises characteristic of the untreated adrenogenital syndrome prevented He also drew attention to the possible virilising effect on female infants when the mother is treated with progesterone during her pregnancy

Turning next to gonadal dysgenesis, he pointed to its relationship with coarctation of the aorta The ætiology is not known

In male pseudohermaphroditism there is deficient interstitial-cell development with a consequent trend towards femininity in development

The testicular feminising syndrome usually associated with the name of Kleinefelter presents the unusual combination of testes, absent uterus, female external genitalia, and normal female stature There is failure of masculinisation of the external genitalia and clumping of the Leydig cells Half of these cases are sex-chromatin-positive and half negative

Exceptionally some spermatogenesis has been noted even in sex-chromatin-positive cases Professor Barr drew attention to the greater frequency of this syndrome in mental defectives and put forward a plea for a closer study of these cases, believing that such a study might lead to some understanding of the causes of mental deficiency—a subject which he maintained had been much neglected by medical research-workers

Uterine Contraction

Dr **ROBERTO CALDEYRO-BARCIA** (Uruguay) reviewed the investigations carried out by the team in Montevideo on uterine contractility by the simultaneous recording of the pressures in different parts of the uterus under different conditions He also presented new work based on the continuous recording of amniotic-fluid pressures in labour He defined uterine intensity of contractions as the difference between the resting and contracting uterine pressures, the frequency of contractions as the number per ten minutes, and the uterine activity as the product of the intensity and frequency, uterine activity is expressed in Montevideo units

As pregnancy advances there is steadily increasing uterine activity until at the onset of labour this amounts to about 100 Montevideo units by the second stage the activity has increased to 250 Montevideo units Distension of the cervix leads to nervous impulses reaching the hypothalamus and then the posterior pituitary with consequent release of oxytocin and augmented uterine action

The simultaneous recording of myometrial activity by microballoons placed in various parts of the uterus has shown up the difference between the normal and abnormal patterns Though the acme of the contractions is reached normally by all parts of the myometrium at the same time, the onset of the contraction starts at the cornu and spreads from here throughout the uterus The pain of labour is caused by cervical distension and later perineal distension Much work on abnormal action was described Hypoactivity of the uterus only led to 40 Montevideo units, and this is not enough to cause labour to progress In such cases a continuous oxytocin drip is used, and the fluid is given with great accuracy by means of an infusion pump

Adrenaline first inhibits uterine activity, and then there is a rebound phenomenon with increased activity Pethidine and morphine have no effect on uterine action Toxæmia is usually associated with good uterine activity Spinal anæsthesia has no effect on normal uterine activity, but if the resting tone of the uterus is high, perhaps because of fear, then it can be beneficial The dorsal position leads to better muscular activity than the lateral positions

Placental abruption raises the tone and no drug has so far been found to lower this, artificial membrane rupture is the best treatment, but it does not lower the tone

If hydramnios with high resting tone is treated by membrane rupture, the tone is lowered and labour is likely to ensue in contrast hydramnios with an initial low tone may be tapped without such a likelihood of labour starting

Dr Caldeyro-Barcia then went on to describe the qualitative faults in uterine action, showing tracings of irregular contractions Several centres of contraction, acting independently, can each have the effect of inhibiting and largely neutralising each other's actions In some cases, at least, intravenous oxytocin in carefully controlled quantity has been found to have a striking coordinating effect Spinal anæsthesia had a similar effect, as did hypnosis

Probably fear and other harmful stimuli adversely influence uterine action by way of the adrenals and by the release of adrenaline and noradrenaline

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Parliament

Ten Hospital Years

As " chairman of Parliament's own hospital ", Lord **Nathan** appropriately opened the debate in the House of Lords on July 2 on our hospitals and their progress during the past ten years The time was, he thought, suitable for such a review, for the start of the National Health Service had in many ways marked a revolution in the social life and habits of the country It had affected vast numbers of the population, and it had influenced the standing and procedures of the medical, dental, and nursing professions It was, perhaps, the central feature of the Welfare State The hospitals were an important part of the service, and he thought that the Ministry of Health and the doctors, nurses, and administrators should be congratulated on the adaptability, assiduity and devotion they had shown in running the hospitals in the unfamiliar circumstances of the last ten years He admitted that he was surprised, though delighted, by the amount of voluntary service still offered At the Westminster Hospital the number of volunteers was greater than ever, which showed that people would not consent to being deprived of the opportunity for service

BRICKS AND MEN

Turning to finance, Lord Nathan said that it had been a period when " I would " had had to wait upon " I can ", and he was uneasy lest capital expenditure be unduly restricted In the past years when money was scarce there had been a tendency to plan hospitals as small as might be, but, though the need for beds had not grown, Lord Nathan suggested that, with the coming of new techniques, the need for more space had grown greatly He urged the Ministry when building new hospitals not to limit their building to the space actually needed at the moment but to exercise imagination and provide for the fresh disciplines and methods of tomorrow We could not retain in this country the young men on whom the future of medicine depends unless we offered them the opportunity of developing their powers and their careers Lord Nathan doubted whether the Ministry was justified in asking hospitals to contribute, for buildings, money from their endowment funds private funds were being used to subsidise expenditure for which Parliament had made the Ministry responsible

Lord **Amulree**, speaking as a member of the medical staff of a London teaching hospital, agreed that during the past ten years the hospital service had improved Many hospitals which had been rather poor were now very good, and there had been no corresponding falling-off in the work of the good hospitals But he was a little frightened about the future If too rigid a ceiling was placed on the amount of money available, then we were bound to get some kind of falling-off Medicine was expensive work to carry out properly, and though one could economise one could not avoid spending money At present there were many drawbacks in hospitals—for instance, operations had greatly increased in number and complexity, and many surgeons were now working under conditions of discomfort if not of difficulty But, provided the staff and equipment were good, he did not think it necessary to have brand new buildings to do good work, nor did he think that there was great need for more beds than at present On the other hand, there was need for more accommodation for infirm elderly people who required care, though not in hospital

Lord **Evans**, in a maiden speech, said that his interest and occupation was with bedside medicine rather than administrative medical affairs He was sure that the quality and standard of medicine must depend on the quality of the teaching hospital, and he pointed out that the teaching hospitals train most of the teachers of the ancillary services as well as undertaking their primary duties of the care of patients, the teaching of medical students, and research Since the start of the N H S little had been done for teaching hospitals save the provision of funds to keep the machinery going They had outmoded inadequate accommodation for patients, teaching, and research Of the twelve London teaching hospitals only two had ever been rebuilt, yet many had been badly blitzed during the war Surely, he said, there must be some limit to the enjoyment of such austerities Surely it was absurd for the teaching hospitals virtually to mark time till every other hospital caught up The immediate past president of the Royal College of Surgeons of England [1] had suggested that hospitals should be encouraged to seek additional sources of finance outside the Government budgets of the N H S For the teaching hospitals, to the minds of many, this would be a welcome return to old practices and in keeping with their heritage In appealing to the community, to industry, and to philanthropic individuals they would follow the example of the universities, and such efforts might enable us in a few years to see several new teaching hospitals in this country

Lord **Moran** said that it was dangerous to measure the progress of a science by the foot-rule of the administrator, but he thought it just to congratulate the Ministry on a remarkable administrative achievement They had decentralised the consultants in this country Because consultants were paid for their hospital work it was no longer necessary for them to live in the great centres, and in almost every part of the country there were now specialists in every branch of medicine Their number had also been greatly increased Moreover the patient could not only see a consultant in hospital, if he was too ill to go there he could call a consultant to his house, and in 1956 there were 265,000 domiciliary consultations Decentralisation had also made possible the upgrading of hospitals throughout the country These two reforms would by themselves have justified the existence of the N H S, but the conditions in mental hospitals had also been transformed Doors had been unlocked, the padded room was a thing of the past, 80% of the patients were voluntary boarders, and outpatient departments had been opened People from America, the Commonwealth, and all over the world came to see how these institutions should be run, and it had been done without rebuilding

REMUNERATION AND OPPORTUNITY

Another reform, Lord Moran continued, which the N H S had brought was concerned with the remuneration of consultants Before the service the consultant obtained his remuneration from private practice Now most consultants got their remuneration for hospital work A man about 40 would get £3255 per annum as a maximum basic salary, and for the rest of his working life he would get no more unless he was given a merit award His material prosperity now depended on his professional efficiency, whereas formerly it was dependent to a great extent on his personality There had, Lord Moran said, been many arguments for and against these awards, but of the bodies that had given evidence before the Royal Commission all save one had spoken in their favour Turning to the future,

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[1] See *Lancet*, 1958, i, 1270, *Brit med J* July 5, 1958, suppl p 5

Lord Moran said that it was important not only that we should get the right quality of men into medicine, we should reward adequately those who submitted to the discipline and years of training to become a consultant If the proper balance between the pay of the consultant and that of the general practitioner was not maintained, recruitment would wither In the last resort the efficiency of the service would depend not on administration but on the quality of the entry and the training of the students He admitted that he was uneasy about the quality of the entry Not long ago middle-class parents paid for the fees of all medical students Now two-thirds were maintained by the State and were selected by examination without any test or regard to character He believed that one could not select people solely on examination for a profession like medicine which required the human touch more than almost any other

He admitted that there was considerable discontent at present among general practitioners but he did not believe it was based on remuneration The cause was to be found in the general decline of the status of general practice It had begun when people who were seriously ill began to feel that they were well advised to go into hospital It was mortifying to the doctors to find that the patient in a crisis preferred to put himself in the hands of a complete stranger The N H S had exacerbated this because, with consultants on their very doorstep, the general practitioners were unable any longer to make those modest excursions into the consultant field which had lent flavour to their life In his view the remedy was for the pick of the general practitioners to follow their patients into hospital and to become part of the staff of the hospital He believed that this should be the most important administrative move in the next decade If that was not done, with a discontented profession, efficiency must wither, whatever the remuneration

The Earl of CRANBROOK shared Lord Moran's hope that the general practitioner should be brought more and more into the hospital But his own feeling was that the hospital needed to be brought more and more outside itself and into contact with the general practitioner and those who were serving the public in their homes

ADMINISTRATORS, BOARDS, AND COMMITTEES

The Earl of LUCAN raised the question of hospital administrative staff The Hall report had shown that the service was not offering a sufficiently attractive career to get the best type of administrator Yet those who were responsible each year for several hundred million pounds of public money should be of the highest quality On the training side there was a serious gap A national scheme had been started a year or two ago, but the number of students was 24 and the course lasted three years It could make only an infinitesimal contribution to the staffing problems of the 400 hospital boards As a result, all the training these young men usually received was by being attached to different departments and different hospitals It seemed to him that much more systematic and positive training was needed Turning to the vexed question of capital investment and hospital building, Lord Lucan said that when he saw the millions of pounds being spent on office buildings, which were often put up for prestige purposes, he wondered if historians in a hundred years would not be puzzled how we could have got our priorities so wrong

Viscount ASTOR asked for an inquiry into the administrative system of our hospitals He felt that most hospital committees were far too big and that the work could be done by half the number of people in half the time Members went into far too great detail on many minor matters which in ordinary administration should be done by a staff, and at the same time the ordinary house-committee had practically no responsibility for the hospital which it was supposed to know intimately The hospital management committees were too big and proliferated so many subcommittees that it was difficult for any busy man to be a conscientious member He believed that we needed small committees, meeting perhaps half as often, with chairmen and officials having greater responsibility for many minor decisions We should try to recruit our hospital officials from a rather wider circle and be prepared to bring in some of those of great administrative ability who were being "axed" from the Services but yet had leadership and knowledge of organisation of people

Another point was the almost complete separation of the medical and lay side Some doctors sat on the management committee but no layman knew anything of what went on at the doctors' committees So there were two parallel chains of committees both looking after the same hospital, "If one suggests that even the chairman of the hospital committee should go to the doctors' committee—well, my word!" He believed that there should be far greater confidence and mutual knowledge than at present

THREE ACHIEVEMENTS

Lord STRATHCLYDE, replying for the Government, suggested that the magnitude of the undertaking was worth a little thought There were in the hospital service in Great Britain some 3700 hospitals and clinics employing 374,000 full-time and 94,000 part-time staff, handling 4½ million inpatients and some 56 million outpatient attendances, and spending something like £400 million in a year It was hardly to be expected that an undertaking of this size, financed from public funds, should not have thrown up many problems during the years in which it has been taking shape, but it would be grossly unfair to all the people running the service to give the impression that the Government were so preoccupied with the problems that required solution and the possibilities of the future that they had no time to spare for appreciation of what had already been done Looking at the whole picture from the point of view of the central Government three features were notable

First, the coming of the hospital service had resulted in specialised medical skill being much more widely available throughout the country The number of specialists employed in the hospital services in Great Britain at the end of 1957 was not far short of 8000, an increase of nearly 33% on the figure even at the end of 1949 when the hospital service had already begun to make its impact Mental health especially had gained by this It was true that we still had not all the specialists we should like in this field, but an entirely new approach to the problems of mental illness has manifested itself in recent years

The second feature was the sheer volume of the work that had been handled, compared with the very limited physical expansion that had been found possible In these last eight years the number of inpatients had risen by 29% in England and Wales, and 43% in Scotland There had been a 6% increase in the number of beds but this had been largely achieved, not by new building, but by bringing into use beds which were formerly idle He did not want to give the impression that the Government did not consider that new building was necessary, but he thought it fair to give credit to the doctors, nurses, administrators and who, despite shortages and obsolescence, had yet achieved so much

The third achievement was the progress made in the integration of the service In 1948 nearly 3500 hospitals were taken over—many completely independent and separate, and others grouped only within a local-authority area He had no doubt that there were still instances where it was far from perfect, but the service today was a reasonably coherent entity and not just a collection of individual hospitals

Amendment of Registration Procedure

On July 2 Lord COHEN OF BIRKENHEAD introduced in the Lords the second reading of the Medical Act 1956 (Amendment) Bill which removes certain anomalies of the present system of medical registration.[1] He informed the House that the Bill had passed all its stages in the Commons without dissent, and that all interested parties had concurred in its provisions

Royal Assent

The Opticians Bill and the Disabled Persons (Employment) Bill have received the Royal Assent

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[1] See *Lancet*, 1958, i, 1340

QUESTION TIME

Hospitals Staffing Working Party

Mr Kenneth Robinson asked the Minister of Health whether it would be open to this Working Party to make recommendations on the levels of consultant staffing either in the country as a whole or in particular regions, and approximately how long he expected the Working Party would require to complete their task —Mr Derek Walker-Smith replied As the Working Party's task is to study the principles on which the medical staffing structure in the hospital service should be organised, they will not be concerned with the numbers of consultants as such No estimate can be made yet of the time they will require, but I am sure they will proceed as quickly as they can Mr Robinson Does the Minister not appreciate that the level of consultant staffing is a basic consideration, not only to the senior registrar problem but to everything else that the Working Party is supposed to be examining? Does he not realise that unless they can recommend on this matter these distinguished gentlemen will be wasting their time?—Mr Walker-Smith It is for these distinguished gentlemen themselves to decide what matters they will need to go into so that they can discharge the terms of reference, of which they are aware and which they have accepted

Mr Robinson asked the Minister why he did not include either a psychiatrist or a layman with special knowledge of the staffing structure requirements of the mental hospitals among his nominees on the Working Party —Mr Walker-Smith The reason is that the Working Party as constituted is well equipped to cover the hospital service generally and is free to obtain evidence about particular classes of hospital, mental and others Mr Robinson Is the Minister not aware of the indignation which is felt among psychiatrists at the way they have been excluded from this important body? Does he not realise that the needs of the mental hospitals, even concerning the staffing structure, may be very different from those of general hospitals? Will he not reconsider the matter?—Mr Walker-Smith I am not aware of any such indignation To give representation to all the various specialties and to the different kinds of hospitals which would logically follow, would only increase the size of the Working Party far above the number of 12 and would certainly have delayed the results of its proceedings Dr Edith Summerskill This is a curious omission, because the hospitals which are grossly overcrowded in every area are the mental hospitals The main problem very often is lack of staff or the proper allocation of staff Therefore, to omit a psychiatrist from a committee which is considering the overall allocation of staff is a little peculiar —Mr Walker-Smith The Working Party consists of people all of whom have great experience in the hospital service They can, I am sure, be trusted to obtain such information as they will need in regard to all the particular classes of hospitals and specialties with which they are concerned Mr Robinson In view of the unsatisfactory nature of this and the previous reply, I give notice that I will raise the matter on the adjournment

Inspection of Imported Egg Products

Mr Arthur Blenkinsop asked the Minister what action he was taking to ensure that imports of egg white were fully inspected before release to manufacturers —Mr Richard Thompson, parliamentary secretary to the Ministry, replied Port health and other local authorities have been asked to pay special attention to the sampling of imported egg products for bacteriological examination At present the authorities try, whenever possible, to sample every batch It would not, of course, be practicable to sample every tin Mr Blenkinsop Does the Minister not agree that the reports from his own Ministry show there is a large proportion of samples taken which show a high level of infection?—Mr Thompson Yes, we recognise that there is a problem here, but we consider that the present arrangements for sampling are the best we have tried and also that the wish which we have made known to the exporting countries ought to provide a solution

In England Now

A Running Commentary by Peripatetic Correspondents

In our early youth we were sick on the second storey of the Eiffel Tower, and since this incident we have had little taste for heights It is difficult to persuade us to enter an aircraft or even to paint the dining-room ceiling, and on our seaside holidays we are a skeleton at the feast While our dependants skip gaily along the smugglers' path, dislodging loose stones into the gulf 300 feet below, we are to be found progressing carefully on hands and knees, gripping the landward vegetation in an ecstasy of spasticity

We were therefore disturbed to find during our last summer holiday that family opinion had committed us to visiting a lighthouse Our confidence in the outcome was not enhanced after we had battered our way in a 50-knot wind to the foot of the structure, by the discovery that we were expected to sign away our chances of survival in advance "I the undersigned", said the form sombrely, "hereby acknowledge agree and undertake for myself and for and on behalf of all minors noted hereunder as under my sole charge that no action suit claim or demand shall lie or be made or instituted in respect of any accident death injury loss or damage sustained or occurring by or to us or to any of us during the said visit I will indemnify", went on the form, clinching the matter, "keep indemnified and save harmless all departmental servants officers and agents against all actions suits claims and demands "

The lighthouse-keeper was sleeping, and his assistant was seeing a man about a wreck, but trustingly permitted us to make the ascent unaccompanied The minors under our sole charge occupied themselves happily in counting the 329 steps, and no accident death injury loss or damage was sustained or occurred on the way up In the lantern room, however, the rarefied air and the presence of several other minors had the worst possible effect Within seconds the lens holder, bearing the legend ON NO ACCOUNT TOUCH THE LENS HOLDER, had been seized and was rotating madly on its axis to the accompaniment of wild cries of exaltation A dissipated-looking minor of a reflective turn of mind had begun to try to drop marbles on the head of the assistant keeper, and a small ginger group was running at high speed round the outside gallery, restrained from falling into the immeasurable depths only by a single rail at chest height After one vertiginous glance through the open door we were forced to concentrate on the lighthouse keeper's box of dyspepsia tablets under the map of the local rocks and reefs While we were thus engaged, the door to the outside gallery slammed and locked itself, the minors under our sole charge, happening to be on the wrong side at the crucial moment, set up a prolonged bawling With set and pallid face we descended the steps to fetch the assistant keeper with a key

When order had been restored and we had indemnified and saved harmless the assistant keeper, we reached the ground again in an atmosphere of mutual congratulation Only too soon a rough count established the fact that our personal quota of minors had been reduced by one Elected a search party by popular acclaim, we climbed the 329 steps for the third time, to find our youngest minor flat on her stomach in the lantern room, deeply immersed in the lighthouse keeper's *True Love Stories* and sampling his dyspepsia tablets

For our next holiday we are going to the Cotswolds

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I suppose this week most of us have been looking back over the past decade and asking ourselves how we have fared According to the popular press we G P s have had a raw deal We are the underdogs of the health service and our yelps for fair play against those bloated plutocrats the consultants should wring the heart of every honest man We work twenty-four hours a day We even have to pay to get a holiday We are bullied by our patients and are treated with contempt by the hospitals

Why then, despite all these horrors, are there dozens of applications for every vacancy in this underdog service?

Is it possible that the Press is not quite accurate in its accounts of our miseries? Perhaps some of us do see eye to eye with our friends the consultants. Perhaps, though of course we wouldn't mention it, most of us love our work. Perhaps we enjoy treating our fellow men in their own homes, even though it means long hours and short holidays. Perhaps, though we hardly dare whisper it, some of us feel that general practice has gone forward during the last ten years and we are proud of it.

* * *

Everyone knows how enlightened and progressive mental hospitals are these days, but I was still unprepared for the reaction of a colleague who was trying to interview patients, in what would once have been called a "back ward", despite frequent interruptions from a character who in a less permissive era would almost certainly have been stowed safely away in a padded cell. Losing patience at last, he flung down his pen and exclaimed indignantly, "Really, Sister, this place is getting to be like a madhouse."

* * *

It is obvious to those who read the literature that getting satellites into space is a matter of stages. We didn't actually get anything into orbit. Initial trials were carried out with 6d and 3d rockets. The smaller rocket was fixed to the larger so as to allow only an upward separation. Firing of the second stage was by a predetermined length of catherine wheel, which was inserted into the vitals of the smaller rocket. When the bugs had been ironed out of this phase the final trial was carried out with a 2s 6d, a 1s, and a 3d rocket. This is only one stage short of space according to junior's calculations. We were reduced to one test vehicle because of lack of enthusiasm in the female part of the family, who did not like catherine wheels being cut up and refused to allow more than one 2s 6d rocket.

This was fired on Guy Fawkes night last year. The count-down went according to plan. The first stage was fired as the fuses of the other two were lit. Unfortunately the smallest rocket fell off, its connections being apparently strong enough only for 6d boost, but the other two stages were away. The end of the first boost was marked as planned by a display of green stars. There was a delay of the cut-in of the next motor, probably because we had to use a different make of catherine wheel to our usual. The second stage could be just seen as a faint gold spot curving over and gradually increasing speed as it fell. Nearing the ground it burst into life and gathering momentum at an alarming rate hit a distant neighbour's roof and disappeared. There was a far-off crash of falling tiles, then silence. The third stage burst into life and vanished into the potting shed. We crept indoors. We are now talking to our neighbour again. It had gold stars, apparently.

* * *

BEFORE AND AFTERTHOUGHTS

I thought I saw an A-line
A-twisted all awry.
I looked again and saw it not
—I cannot tell you why.

I thought I saw a Newton
In thought upon the shore,
I looked again and saw it was
A man I could ignore.

It seemed I saw a System
Of thoughts all bright and new,
I looked again and saw they were
A muddled, motley crew.

I thought I saw Time's chariot,
Wing'd horses all before,
But after, when I looked again
They were in front no more.

Had we but world enough and space
These theories, Doctor, were in place,
Do write again, but ere you start
Put Reason's horse in front of Fancy's cart.

Letters to the Editor

ORTHOPÆDICS, INDIVIDUALITY, AND THE HOSPITAL SERVICE

SIR,—At a time when we are reviewing the work of the past ten years I should like to stress the tradition of individual effort and the difficulty of giving it expression in the hospital service today. The difficulties are largely inescapable when control is in the hands of coordinating committees and administrators largely out of personal touch with the day-to-day work of hospitals and for whom organisation, centralisation, integration, and rationalisation are prominent thoughts. Tradition should not slavishly be followed: many traditions hold bad features. The Ministry of Health has, however, been right in emphasising the need to preserve the good traditions of the voluntary hospitals (though it is often very difficult for the house committees of these hospitals themselves to maintain them). The idea often is given no more than lip service.

I am worried by the discouragement of a sense of responsibility and initiative at the periphery and particularly worried by a tendency to destroy certain valuable schemes of hospital service which, in advance of their day, were built up by the enlightened and creative efforts of pioneers like Robert Jones and Henry Gauvain. Naturally I take the orthopædic service, for it is the one I know best and because (as I pointed out in *The Lancet* in 1944[1]) it possessed features which we can now see foreshadowed many of the developments of the national hospital service itself.

It is unfortunate that orthopædics is often thought of as a purely surgical special branch of medicine. If it were so there would be some excuse for regarding the orthopædic idea of segregation, teamwork, continuity of treatment, and rehabilitation as an anachronism in special hospital units. On the contrary, orthopædics is a very general rather than highly specialised branch containing a dominant interest in medicine itself. Sir Henry Gauvain, who started his work at Alton fifty years ago, exemplified one aspect of this physician's outlook and he built up a splendid institution. At Oswestry, Oxford, Stanmore, and Pyrford similar organisations were established by the pioneers. They involved a compact organisation of a central hospital fed from and feeding into dispersed outpatient clinics with a team of surgeons and their specially trained groups of aftercare sisters, orthopædic nurses, secretarial staff, workshops, &c. In each the emphasis varied and the model was that at Oswestry. These schemes and others like them (and indeed others which still should be established) have a special approach to the whole man (starting with childhood), his social background, and the continuity of his treatment leading to rehabilitation.

The compactness of the organisation with its individual leadership and fine teamwork is now faced with a changing clinical responsibility. Although tuberculosis, rickets, osteomyelitis, and we expect, poliomyelitis are diminishing, nevertheless the congenital and developmental anomalies of childhood, trauma, arthritis, and the locomotor lesions of stress will continue to provide a large number of long-term problems for which treatment in these schemes is well found. It would not be right to say that there is great overt evidence of destruction, yet in this-and-that small way orthopædic institutions are being eroded. There is loss of individual identity, and the consequent weakening of morale, lack of proper support for the training and wellbeing of the orthopædic nurse and aftercare sister, and the separation of sections of the work of an organisation into the hands of new consultants working largely in isolation from the parent team, which results in dispersal of clinical material.

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[1] Capener, N. *Lancet*, 1944, ii, 355.

This dispersal may be considered to be countered by the association of the orthopædic surgeon with his general medical and surgical colleagues in local units and by the association of the patient's treatment nearer his home. Of course orthopædic surgeons should be part of the team in every general hospital, but this need not be incompatible with his belonging to another team as well A patient's separation from the neighbourhood of his home has disadvantages but is less of a problem now than it was thirty years ago, and in any case is outweighed by the advantages of the greater experience and skill to be achieved in the special hospitals, particularly when these have an efficiently coordinated aftercare clinic system.

I am not so senile as to think that these orthopædic-hospital schemes could not be improved What I do say is that it is very difficult to do the necessary individual creative work in the atmosphere of central group administration.

There is one final point The orthopædic services of this country are the envy of foreign visitors, who so often have nothing of the sort. We owe it to the new Commonwealth nations to maintain and develop this type of organisation Abroad they still see tuberculosis and other crippling diseases in the dreadful form that we did thirty and more years ago, and their young men come to us to learn

Exeter NORMAN CAPENER

N H S STAFF COLLEGE

SIR,—The suggestion from Dr Parker (July 5) of a National Health Service Staff College is to be warmly welcomed We should, however, hesitate before advocating a Staff College exclusively for members of the profession We need to see an end to the rivalries for administrative authority At the last annual conference of the Institute of Hospital Administrators, it was sad to hear how much time was given to discussion of who was responsible to whom This, no doubt, is a natural preoccupation among lay administrators still looking over their shoulders to the days when medical superintendents were all-powerful figures in every aspect of hospital responsibility, but it is an attitude which stultifies initiative and innovation

The most advanced sectors of industry today have long recognised the vital contribution which technical training and background can make to administration The second industrial revolution we are witnessing today is being directed by a partnership of " lay " and technically trained management, applying the new knowledge of technology, operational research, and social science with an effective enthusiasm from which the Health Service has much to learn

After ten years of reaction against medical administration in the service, a new balance needs to be reached and a working partnership created between medical, nursing, and lay personnel An exclusively medical staff college may accentuate rather than resolve the existing divisions

The Administrative Staff College of the King Edward Hospital Fund is carrying out an imaginative and stimulating task, almost entirely among the lay staff of management committees The fund also runs a college for administrative nursing staff Could not the present Staff College be expanded to cater jointly for medical and other administrators ? I believe that a Joint Staff College, in addition to its function of training in the techniques of modern management applicable to a health service, would do much to define each partner's proper sphere of activity, and to infuse that sense of common purpose which the service so badly needs

Paddington General Hospital,
London, W 9
J FIELDING
Medical Director

DEATH OF A BOXER

SIR,—I have followed the correspondence upon the medical complications of boxing with mixed feelings Dr Lyburn's last letter (July 5) goads me into reply, however

Surely among his boxing friends and acquaintances he has encountered traumatic progressive encephalopathy There now exists really quite a formidable literature upon the subjects of punch-drunkenness, on death in or shortly after a boxing bout, as well as on the occurrence of subdural hæmatomata and of traumatic carotid occlusion as a result of boxing The ophthalmic literature alone contains an impressive record of injuries to the eye

London, W 1 MACDONALD CRITCHLEY

REVERSAL OF SUXAMETHONIUM PARALYSIS WITH NEOSTIGMINE

SIR,—Dr Shegog Ruddell reports an instance of neostigmine-reversible suxamethonium paralysis in a child, and demonstrates once more that anticholinesterase decurarising drugs may be used with confidence in these circumstances[1]

In 1954 I drew attention to the fact that young children were inherently resistant to suxamethonium,[2] and in 1955 confirmed this, showing that the characteristic was unrelated to cholinesterase activity, and probably associated with no physical factor other than an inherent " state "[3] I am sure that had the biochemical estimations, including the serum-cholinesterase, been forthcoming in Dr Ruddell's patient, they would have been essentially normal More recently, with others, I suggested that changes in sensitivity to depolarising relaxants were more likely to occur in those patients showing an inherent resistance to the drug in the first instance[4] The clinical sequel of these two observations (that the young are prone to develop a " dual " response after depolarising agents) has been noted by Rees[5]

Better terminology would clarify the situation in the minds of many of us The terms " depolarising " relaxants, and " dual " response are misleading The expression biphasic response, illustrating consecutive rather than concurrent actions, would seem preferable[6] The second phase of this response represents the typical, and to be expected, non-depolarising effects of the so-called " depolarising " agent, and may be recognised and treated as such with confidence

In the presence of a raised endplate resistance to depolarisation the typical action of suxamethonium, already previously described,[7, 8] is slower in onset, less intense in effect, but mildly prolonged In this phase, if attempts are made to obtain (with the less effective agent) the immediate and profound relaxation usually associated with the depolarising action of suxamethonium, accumulative effects and further delay in recovery may follow This depression is reversed by anticholinesterase drugs

These circumstances do not contraindicate the use of suxamethonium, providing it is recognised that a slightly longer-acting and less effective " non-depolarising " agent is being administered, and precautions are taken to avoid overdose Antidotes should be used whenever indicated

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[1] *Lancet*, 1958, i 1390
[2] Hodges, R J H, Harkness, J *Brit med J* 1954, ii, 18
[3] Hodges R J H *Proceedings of the World Congress of Anæsthesia* *Curr Res Anæsth* 1956, p 247
[4] Foldes F F, Wnuck A L, Hodges, R J H, Thesleff, S, de Beer, E. J *ibid* 1957, 36 23
[5] Rees, G J *Brit med Bull* 1958 14, 38
[6] Hodges R J H, Foldes F F *Brit med J* 1957, i, 373
[7] Hodges R J H *ibid* 1956 ii 1240
[8] Hodges, R J H *ibid* 1958, i, 1416

A non-depolarising block following the administration of suxamethonium may be anticipated not only in children and neonates It may be expected to arise whenever endplate resistance to depolarisation is present, inherently as in certain species, pathologically acquired as in myasthenia gravis and sometimes electrolytic imbalance, or induced (particularly in those with an inherent tendency) by drugs. This last may follow the administration of relaxants,[4] but may also follow the administration of drugs with no obvious clinical neuromuscular-blocking effects (e.g , oxytocin) [5]

Portsmouth **R J HAMER HODGES**

ANÆSTHESIA FOR THE EMPHYSEMATOUS

SIR,—In an annotation [1] you summarise the hazards of general anæsthesia and artificial ventilation in emphysematous patients The article goes on to say that despite its drawbacks artificial ventilation " is generally advisable for emphysematous patients undergoing extrathoracic operations as well [as thoracic operations,] since it is the only means of ensuring adequate gas exchange "

It is unfortunate that your article dealt exclusively with general anæsthesia, and that regional anæsthesia, either alone or in combination with light general anæsthesia, should not have been mentioned, for the latter provides good operating conditions, as well as adequate respiratory exchange in most cases Admittedly, in thoracic and upper-abdominal operations under regional anæsthesia, suppression of intercostal activity demands the use of controlled respiration just as in non-emphysematous patients, but in operations elsewhere adequate spontaneous respiration can usually be retained, if in doubt ventilation can be measured directly by switching a simple spirometer into the anæsthetic circuit from time to time

The retention of adequate spontaneous respiration has definite advantages, for while it exists the normal inflationary pattern of the chest is maintained, and alveolar ventilation-perfusion ratios remain relatively unaltered. But, as Campbell et al [2] point out, the imposition of artificial respiration is accompanied by an increase of physiological dead-space, and the hazards outlined in your article are added to this Besides the difficulties you mentioned there is some evidence that under light general anæsthesia and neuromuscular blockade surgical stimulation reduces the compliance of the lungs, so that the work of breathing is increased, and higher intrathoracic pressures have to be used to shift a given volume of gas [3]

The neuromuscular-blocking agents have made general anæsthesia so simple and safe that the pendulum has swung away from the more exacting methods of regional anæsthesia, which are falling into disuse Consequently, the present generation of anæsthetists-in-training find it difficult to obtain a good practical grounding in regional techniques, although these still have much to offer, especially in the emphysematous patient. Unfortunately skill in regional methods requires practice, and this is not always easy to obtain when slickness of " throughput " is so often the primary aim in many operating-theatres But consultant anæsthetists should see to it that their juniors do get the opportunities to achieve facility with regional techniques, otherwise the disciplines of the specialty will become depressingly narrowed.

Royal Victoria Hospital,
Montreal **P R BROMAGE**

SIR,—The remarks in your annotation of June 14 are very timely Extensive experience has shown that artificial respiration is imperative for all such patients undergoing major operations under general anæsthesia—regardless of the site of operation

A few points may be re-emphasised the administration of bronchodilator drugs should be an integral part in the maintenance of anæsthesia, and the rate of respiration and tidal volume should be monitored, together with the airway pressures These parameters may be accurately determined before induction of anæsthesia on the basis of the size and age of the patient, together with an estimate of degree of emphysema (simply determined by the breath-holding test and expiration time) [1] These must be adjusted according to the posture assumed by the patient to facilitate the work of the surgeon [1]

When these measures are employed, emphysema presents no problems in oxygenation or carbon-dioxide elimination, and spontaneous respiration is resumed quickly at the end of the anæsthetic if care has been taken to establish a light level of analgesia, hypnosis, and muscle relaxation.

Department of Anæsthesia,
University Hospital,
Saskatoon, Saskatchewan **ALLEN B DOBKIN**

LIPOPROTEIN PATTERNS IN MYOCARDIAL INFARCTION

SIR,—In reviewing the excellent article by Dr Elspeth B Smith [2] I was much impressed by the correlation between the characteristic lipoprotein band, the pre-β-lipid found associated with myocardial infarction, and the S_f20–100 part of the standard S_f12–400 class of lipoproteins of Gofman

In our attempts to reverse existing atherosclerosis and to lower the levels of both S_f0–12 and S_f12–400 lipoproteins, as well as cholesterol levels, it has been virtually impossible to lower the S_f20–100 and the S_f100–400 parts of the standard S_f12–400 class of lipoproteins without carefully screening out all products of hydrogenation.

Niacin (nicotinic acid), fresh thyroid extract, low-natural-saturated fats and low-cholesterol intake, plus 2–3 ounces daily of corn oil (mazola) or 12 capsules daily of 750 mg safflower oil by mouth, have been given to supply additional unsaturated linoleic acid. All products of hydrogenation were excluded, and replaced in all baked or fried foods by the essential unsaturated linoleic acid in the form of corn oil By this means it has been possible to reduce rapidly cholesterol and both groups of lipoproteins

Nicotinic acid was given in total daily dose of 3 g divided and after meals, and the fresh thyroid extract was started at usually no less than gr 3 and raised to gr 6 or more depending upon the lipid-lowering response

All our lipoprotein patterns were air-mailed the same day to the Gofman group at the Institute of Medical Physics at Belmont, California, for ultracentrifuge analysis, and all patterns are there recorded by number Dr Holly Heitzman, clinical director of St. Mary's Hospital, Green Bay, secured the blood samples for a portion of this study, and Dr John Ford, clinical director of St Vincent's Hospital, Green Bay, secured the remaining group of blood samples Both hospital groups are now correlating the total cholesterols, atherogenic indexes, and diastolic and systolic pressures

The following is a typical case, in which the intelligent cooperation of the patient was secured in this simple approach to the possible reversal of atherosclerosis

A 53-year-old woman weighing 163 lb had a blood sample taken on March 12, 1958 fasting cholesterol 200 mg per 100 ml , S_f0–12 413 mg per 100 ml , S_f12–400 844 mg per 100 ml , atherogenic index 189, blood-pressure 190 110 mm. Hg

On May 1 the findings were weight 146 lb , fasting cholesterol 140 mg per 100 ml , S_f0–12 245 mg per 100 ml , S_f12–400 62 mg per 100 ml , atherogenic index 35, blood-pressure 104 76 mm Hg

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1 *Lancet* 1958 i 1261
2. Campbell, E J M , Nunn, J F , Peckett, [illegible] *Brit J Anæsth* 1958, 30, 166
3 Bromage P R. *Clin. Sci* 1958, 17 217

1 Dobkin A. B *Brit J Anæsth* 1958, 30, 282
2 *Lancet* , 1957, ii, 910

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Of the utmost clinical significance during this study, which has been correlated with the Gofman group since November, 1957, has been the inability to produce any considerable lowering of the S_f12–400 class of lipoproteins without carefully screening out all products of hydrogenation.

At this point it definitely seems that the unnatural unsaturated fatty acids with a high melting-point, which are the products of hydrogenation, may be a most important factor and in all probability are not reflected in the total cholesterol estimation, and fall into S_f20–100 and the S_f100–400 parts of the standard S_f12–400 class of lipoproteins [3]. There is little doubt that a large part of human disease is due to physiological chemical imbalance, but it is apparent that the body cells can recover to an amazing degree from these chemical upsets.

Green Bay,
Wisconsin

WARREN T HAGERTY

THE ÆTIOLOGY OF LEUKÆMIA

SIR,—Your leading article of July 5 might be criticised on the grounds of incompleteness, but it would not be possible to meet this criticism in less than a large tome. It could be argued that the title was misleading and should have been the Virus Theory of Murine Tumours, and it is certainly odd to find no reference to, among American workers, Kaplan and Law and only one, purporting to support Gross, to Furth. However, accepting the thesis that Gross and Stewart and Friend have produced extremely powerful evidence in favour of viral agents being intimately involved in the development of various murine neoplastic diseases, or, as they might argue, causative, it must seem ludicrous to them to read your conclusions, (*a*) that an impasse has been reached, whereas in fact the field is developing so fast that even you, Sir, seem not to be abreast of recent multitudinous advances, and (*b*) that, an infective agent having now, you infer, been isolated and categorised, there is little that can be done about it. Oh, Koch!

Atomic Energy Research Establishment,
Harwell, Berks

J F LOUTIT

EXPERIMENTAL PRODUCTION OF ENDOMYOCARDIAL FIBROSIS

SIR,—I write to correct a statement attributed to me, by Professor Selye in his interesting paper [4].

I was quoted as saying that 40% of patients with heart-disease, admitted to hospital in Eastern Nigeria, have endomyocardial fibrosis. This statement was apparently based on my personal communication to Dr Brigden, to which reference was made in his St Cyres lecture [5].

What Brigden said was "Nwokolo has seen the condition (of endomyocardial fibrosis) in Eastern Nigeria, where he finds that 40% of cases of heart-disease admitted to hospital are cardiomyopathies." In that lecture, Brigden used the term cardiomyopathy to include obscure cardiopathies such as congenital cardiomyopathy, nutritional heart-disease, alcoholic heart-disease, amyloidosis, collagen diseases of the heart, infective myocarditis of all kinds, endomyocardial fibrosis, and other cardiopathies of unknown ætiology. It is clear therefore that Brigden did not use the term cardiomyopathy to mean endomyocardial fibrosis only, as Professor Selye's usage seems to imply.

In my communication to Dr Brigden, I referred in part to a publication [6] in which I reported cases of endomyocardial fibrosis confirmed at necropsy, as well as other cases in patients who died of congestive cardiac failure but in whom no fibrosis was found at necropsy. The figure of about 40% referred to the proportion of cases of obscure cardiopathies in relation to the total number of cardiac admissions into the General Hospital, Enugu, Eastern Nigeria, in a small series of cases.

My view is that endomyocardial fibrosis constitutes a mere fraction—probably under a third—of these obscure cardiopathies.

London, S W 18

C NWOKOLO

CORTISONE IN THE TREATMENT OF ACUTE MILIARY TUBERCULOSIS

SIR,—I was pleased to read that Dr Lambros [1] has successfully treated a case of miliary tuberculosis using cortisone with the antituberculous drugs.

A case of miliary tuberculosis and meningitis in a patient who was also hypersensitive to streptomycin was included in a series of cases of active tuberculosis treated by corticotrophin and chemotherapy which I published in 1954 [2]. This patient remains completely well six years later.

Harefield Hospital,
Middlesex

L E HOUGHTON

ANKYLOSING SPONDYLITIS AND CHRONIC INTESTINAL INFLAMMATION

SIR,—Forestier [3] and Romanus [4] mentioned an association between ankylosing spondylitis and inflammatory intestinal disease, and Steinberg and Storey [5] have reported 6 cases. I have seen 3 examples of this association.

CASE 1.—A man, aged 31, was admitted to Frenchay Hospital in 1957. He had pain in the lumbar region and left leg, which had started some seven months previously and had been treated, by physiotherapy and a plaster-of-paris jacket, with improvement. He also had diarrhœa, which had started suddenly seven weeks previously, with bowel action 18–20 times daily, very loose, and frequently containing blood and slime. He had had previous episodes of diarrhœa in 1943 and 1944.

The left side of his abdomen was very tender, movements of the lower thoracic and lumbar spine were limited and straight leg raising was restricted on the left. Hæmoglobin was 54%, erythrocyte-sedimentation rate (E S R) 60 mm in the first hour (Wintrobe). Sigmoidoscopy showed a reddened mucosa but no ulceration in the rectum. A radiograph of the spine showed partial obliteration of the sacroiliac joints and some calcification in the anterior spinal ligament, this was regarded as typical of ankylosing spondylitis. A barium-enema examination showed very extensive changes involving almost all the large bowel, and these were typical of ulcerative colitis.

The patient improved on treatment with corticotrophin and was later given a course of radiotherapy to the spine after transfusion had corrected the anæmia.

Diagnosis.—Ankylosing spondylitis and ulcerative colitis.

CASE 2.—A man, aged 59, was admitted to Frenchay Hospital in 1954 complaining of loss of weight and pain in the back and neck of two years' duration. He was pale and wasted, and had considerable limitation of all spinal movements. Hæmoglobin was 70%, E S R 60 mm in the first hour, colour-index 1.3. The marrow showed a few megaloblasts but mainly a normoblastic picture. Stool examination showed definite steatorrhœa. Radiographs of the spine showed fusion of both sacroiliac joints and calcification of the spinal ligaments. Barium-enema examination showed no definite abnormality.

He made good response to treatment with folic acid, iron, and calciferol, and his hæmoglobin rose to 94%. He was later given a course of radiotherapy which eased his spinal pain considerably

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[3] Griffith, W H *J Amer med Ass* 1957, 164, 411
[4] Selye, H *Lancet*, 1958, i, 1351
[5] Brigden W *ibid* 1957, ii 1243
[6] Nwokolo, C *W Afr med J* September, 1955 4 103

[1] Lambros, T A *Lancet*, 1958, i, 1370
[2] *ibid* 1954, i, 595
[3] Forestier J *Radiology* 1939, 33 389
[4] Romanus, R *Acta med scand* 1953, 145 suppl 280
[5] Steinberg, V L, Storey, G *Brit med J* 1957, ii, 1157

Diagnosis —Ankylosing spondylitis and steatorrhœa of unknown cause

CASE 3 —A man, aged 53, was admitted in 1957 to Southmead Hospital for investigation of bouts of diarrhœa which had begun three years previously The motions were at times very offensive and contained blood and mucus He had been under treatment for ankylosing spondylitis since 1946

Spinal movements were much limited and occult blood was present in the fæces Hæmoglobin was 84%, E S R 46 mm in the first hour Radiographs of the spine showed bridging between the bodies of the lumbar vertebræ Barium-meal and follow-through examination showed a definite irregularity of the terminal ileum, of the type seen in regional ileitis

His diarrhœa settled when codeine was given orally, and his general condition improved in hospital

Diagnosis —Ankylosing spondylitis and Crohn's disease

In these 3 cases, chronic intestinal disease was associated with ankylosing spondylitis, and it is my impression that this association is not one of chance

I should like to thank Dr J M. Naish for permission to publish these cases

Department of Medicine,
Frenchay Hospital, Bristol

S G FLAVELL MATTS

THE TOURNIQUET

SIR,—In your leading article of May 31 and in Professor Pannett's letters of March 15 and June 14, certain categorical condemnations of the tourniquet are made While it is true that there is an increasing tendency for limb surgery to be undertaken without the tourniquet, the time has not yet come when it could or should be completely discarded

Professor Pannett's experiences of " enormous œdema when the tourniquet is removed " and his view that " infection is likely to establish itself more easily " are not paralleled by the experience and opinions of many orthopædic surgeons It is possible, for example, to use below-knee tourniquets for foot operations with full hæmostasis but without getting peroneal palsies if the " Esmarch's " bandage is accurately applied Infection of clean wounds is rare in orthopædics and is no commoner in, for instance, knee operations done with a tourniquet than in hip operations done without Again, postoperative œdema need not follow, particularly if the surgeon himself puts on the bandages, not leaving it to the most junior person in the theatre

While I entirely agree with your reiterated warnings on the use of the tourniquet, I cannot agree with ex-cathedra pronouncements (such as " There is no place for below-knee tourniquets ") which can only cause embarrassment to some and give universal condemnation to a procedure which continues to have a place in the right hands

Mr I S Smillie once said, in reply to a charge that one of his instruments was dangerous " All surgical instruments are dangerous unless they are used properly " The same applies to the tourniquet

Canterbury

F G ST CLAIR STRANGE

RECORD OF EXPOSURE TO RADIATION

SIR,—At the present rate of nuclear-weapon tests we shall soon have reached the point of no return as far as the limit of safety to radiation exposure is concerned This is a grim state of affairs about which the medical profession can do little more than indicate the risks and dangers

We have, however, a grave responsibility in deciding whether our patients should be exposed to further radiation in the form of diagnostic X rays I have for long been concerned at the casual way in which these investigations are carried out, usually with no regard to the number and cost of films taken in the past and often with insufficient consideration to the question " is this procedure really necessary ?"

It seems to me that the time has now arrived when every patient should have some sort of simple record card whereon is shown the total amount, as far as it can be estimated, of previous radiation to which he has been exposed and where can be recorded subsequent amounts at the time the films are taken

Royal Salop Infirmary,
Shrewsbury

A W J HOUGHTON

INFLUENCE OF LIGHT ON THE HYPERBILIRUBINÆMIA OF INFANTS

SIR,—I was very interested in the paper on the above subject by Dr Cremer and his colleagues,[1] and their effort to use light for the reduction of hyperbilirubinæmia Their observation that serum-bilirubin is photosensitive was also noted by me and recorded, in a paper on the Technique and Interpretation of the van den Bergh Test, in the *Irish Journal of Medical Science* for September–October, 1927, when I said. " Sera to be examined should not be exposed to bright sunshine "

Dublin

R E STEEN

CERVICAL AORTIC ARCH

SIR,—It would seem desirable to make a plea against the term " cervical aortic knuckle " to describe the aortic-arch anomaly noted by Professor Lewis and his colleagues [2]

It is the summit of the arch itself which is seen pulsating in the neck, whilst " knuckle " might imply an aneurysmal dilatation of the arch which projects The term is undesirable also in that it carries an ætiological suggestion of the aortic arch having spilled or " knuckled " out of the chest Embryological considerations refute this possibility and show that the arch is, in these cases, a cervical structure

In January, 1957, a 35-year-old certified mental-defective man, having a right upper mediastinal shadow on a mass radiograph, associated with a pulsatile swelling on the right side of the neck extending to the hyoid cartilage, was admitted to hospital Compression of the mass produced obliteration of pulses in the right arm and both femoral arteries, whilst those in the left arm remained Manometric tracing of this diagnostic obliteration of femoral pulse was obtained, and the anatomical features of the convoluted, right-sided aortic arch in the neck were demonstrated by retrograde aortography These appearances differed from the post-mortem findings of Beavan and Fatti [3] in that the left subclavian artery arose from a left innominate artery, the first branch of the arch, whilst in their case the left subclavian was the last major branch of the arch No evidence of dyspnœa nor dysphagia could be obtained and the patient remains under observation This case was presented with cine-photography of the swelling by Mr R Abbey Smith at the summer meeting of the Thoracic Society in 1957 and a detailed report and analysis are being prepared

It should be remarked that in all three patients noted to have this condition, the cervical aortic arch has been right-sided, and the descending aorta left-sided Reid [4] described an anatomical dissection in which a right aortic arch " ascends through the superior aperture of the thorax into the root of the neck and must have given rise to marked supersternal pulsation "

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1 Cremer R. J , Perryman P W , Richards, D H. *Lancet*, 1958, i, 1094
2 Lewis, C , Harley, H R. S Rogers L C. *Lancet* 1958, i, 1340
3 Beavan T E D , Fatti, L *Brit J Surg* 1947, 34, 414
4 Reid, D G *J Anat , Lond* 1914 48, 174

Notably, also, the cases of abnormally high thoracic aortic arch recorded by Tori[5] and Mr Norman Barrett's case[6] have been right-sided The embryological grounds for this right-sided nature are perhaps less readily acceptable than the reasons for a cervical arch, and it is noteworthy that, in the offspring of vitamin-A-deficient rats, Wilson and Warkany[7] found the condition twice on the left, three times in a double aortic arch, but never singly on the right, though in all cases there were also other variations of the arch pattern Nevertheless, and at least until a left-sided case is recorded, it seems reasonable to describe the condition now recognised as "right-sided cervical aortic arch"

Dysphagia developing for the first time in middle age owing to ring-like formation raises particular consideration in these cases Both dysphagia and dyspnœa may present during infancy from vascular rings Dysphagia, without dyspnœa, developing for the first time in adult life, usually middle age, is considered to be due to degenerative changes in the wall of the systemic vessel, and is most commonly associated with retro-œsophageal arteries rather than vascular rings Should this symptom develop then in a case of right-sided cervical aortic arch, the possibility must also be considered that it is due to atheromatous changes in the retro-œsophageal descending part of the aorta—especially when, as in our case, a left-sided ligamentum arteriosum, if present, is probably long and anterior—rather than a ring formation

King Edward VII
Memorial Chest Hospital,
Hertford Hill, near Warwick

JOHN C A RAISON

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5 Tori, G *Ann Radiol diagn*, *Bologna*, 1948, 20, 18
6 *In* Congenital Heart Disease, by J W Brown London, 1950
7 Wilson, J C, Warkany, J *Pediatrics*, 1950, 5, 708

Obituary

ANDRIJA STAMPAR

M D Vienna

FROM Balkan peasant to first chairman of the Economic and Social Council of the United Nations and president of the first Assembly of the World Health Organisation—such was the record of Andrija Stampar Like most other men who have made their mark in international health, he first achieved prominence through hard work and advanced ideas in his own country

Born in 1888 in Croatia, he qualified at Vienna in 1911 and from the beginning showed his abiding interest in social medicine He wrote and lectured against the evils of alcoholism, and he remained a lifelong teetotaller After working as a district medical officer in Croatia, he became in 1919 director of public health for the whole of the new kingdom of Yugoslavia in his early thirties and introduced many reforms into the organisation and practice of rural hygiene In 1931 he returned as professor of hygiene to Zagreb, where a school of public health had been founded with the help of the Rockefeller Foundation The essence of his teaching was a two-way traffic by which leading villagers came to the school to be taught simple principles which they put into practice on returning home Such ideas are almost commonplace in underdeveloped rural communities nowadays, but they are only commonplace because of Stampar's initiative and drive

Dr Rajchman, director of the Health Organisation of the League of Nations, was among the first to recognise Stampar's work and worth and secured his help for the Health Organisation in various ways, including membership of the Health Committee of the League He served the League in China from 1933 to 1936 and visited the United States and this country on many occasions The war—and Stampar's Left-wing views—led to his internment in Austria for a time, but liberation found h beloved Zagreb University, of which he was made recto intact if impoverished, and he obtained many supplie and books from friends and sympathisers in this and othe countries

Unique among Yugoslavs at that time in his pre-wa international experience and reputation, he was quickl restored to even greater international prominence an elected chairman of Ecosoc which, at its first meeting i 1946, acted on the decision of the San Francisco conferenc that an international conference should be called t consider setting up an international health organisation o the United Nations

Stampar served on the technical preparatory committe for this international health conference and submitted memorandum on the constitution of the new agency besides taking part in the conference itself It was therefor wholly appropriate that he should have been electe chairman of the Interim Commission of W H O in 19 and president of its first Assembly in 1948 Since tha time until recently he had been associated with the worl of W H O in many ways, and in 1955 he received th Leon Bernard Foundation prize for pre-eminent work i social medicine

A colleague writes

Stampar's success had three elements—technical competence, political flair, and a peasant toughness which, in the polit world of international health, made men chary of offendin him His very appearance inspired a certain awe His cannon-ball head, sunk between huge shoulders, looked as if he coul batter a breach in a wall with it—sometimes indeed he migh have tried to do so to judge from his temper when things had not gone as he wanted! It needed courage, as well as affection, for the chief British delegate to take him by the arm on one such occasion and remark, "Well, you great Balkan bear! How's the sore head this morning?" But all in all he was a great man and his country should be proud of him

Appointments

DEWAR, A E, M B St And, F F R, D M R D assistant radiologist, X-ray diagnostic department, St Thomas's Hospital, London

FRANKLAND A W, D M Oxon part-time consultant in charge of the clinic for allergic disorders (Wright Fleming Institute of Microbiology), St Mary's Hospital, London

HALL, THOMAS M B Cantab assistant M O, Wembley and Willesden

MCEVEDY, B V, M CH Oxon, F R C S assistant surgeon, Royal Victoria Infirmary, Newcastle upon Tyne, and surgeon, Gateshead hospital group

MACINTYRE, J C, M B Glasg, D A S H M O in anæsthetics, Stornoway hospitals

RHODES, PHILIP, M B Cantab, F R C S, M R C O G part time consultant in obstetrics and gynæcology, St Thomas's Hospital and Lambeth Hospital, London

*WILD, A A, M B Edin, D M R D full time consultant in radiology York A and Tadcaster, Scarborough, Bridlington, Malton and Whitby hospital groups

Birmingham Regional Hospital Board

DUNCAN, J McK, M B Birm, F R C S part-time consultant surgeon, Dudley and Stourbridge hospital group

HOOPER, B R S, M B Lond, F F A R C S, D A part time consultant anæsthetist, Lichfield, Sutton Coldfield, and Tamworth hospital group

KALRA, P L, M B Birm, D P M assistant psychiatrist, St George's Hospital Stafford

PORTER, K R D, M B E, M R C S, D P H deputy senior administrative M O to the board

Manchester Regional Hospital Board

ALLEN, W M, M B Manc, D M R D consultant radiologist, Preston and Chorley hospital group

LEWARS, P H D, M B Durh, B D S senior hospital dental officer, South Manchester hospitals

MARTIN, W M, M B Belf assistant anæsthetist, Burnley and district hospital group

* Amended notice

Notes and News

EXTENSION TO BIRMINGHAM MENTAL HOSPITAL

ON June 26 Dame Enid Russell-Smith, deputy secretary of the Ministry of Health, opened two 40-bed pavilions at Hollymoor Hospital, near Birmingham.

The new buildings, which are about a quarter of a mile from the main buildings, stand on a southern slope, and have been designed on one floor so that the open outlook from the hospital is unimpaired The two units are linked by a kitchen with its own service entry The dayrooms and dining rooms of each unit are next to the kitchen They have low window sills to make the best use of their southern aspect and view of the Lickey Hills, and open fireplaces of natural clipsham stone Each unit has two 20-bed dormitories linked by sanitary wings which are also accessible from the day rooms Light, cheerful colours have been used for walls, door, and curtains, neutral shades for the rubber floors, rugs, and furniture The scheme was designed by S N Cooke and Partners in association with Mr D A Goldfinch, architect to the Birmingham Regional Hospital Board

After the opening ceremony plaques were unveiled commemorating the work of Dr S J Scurlock, who has lately retired from the post of senior administrative medical officer of the Birmingham regional hospital board, and of Dr T A. Lambo, psychiatrist to the Aro Hospital in Western Nigeria, who is cooperating with the hospital in the training of Nigerian student nurses

ECONOMY IN PRESCRIBING

THE Ministry of Health has accepted the view, expressed in the interim report of the Committee on the Cost of Prescribing,[1] that the supply by executive councils of medical and pharmaceutical lists to drug houses is undesirable The Ministry has asked any executive councils that hitherto have provided lists in this way to discontinue the practice.

University of Manchester

At recent examinations the following were successful

M.B, Ch.B—J W Aspinall, Roy Battye, F H Brindle, D B Brockes, J E Brooks, A L Buckley Eric Charles, P J Cox, J S Cumming, Barry Deakin, B H Delany G G Duckworth R M Flinn, Joyce Harris, Roy Haworth, Patricia A Hegarty, Raymond Holmes, Alexander Hopkins W H. Isbister, Maria Z Kozubowska, R. J Lawton I P McEwan, A C. Petersen, J D Rhodes P H Roberts, Martin Ryan, Elizabeth M Spencer, Roy Statham, Garo Tahta Peter Watson, J M Watts, B K. Wignall, J D G Williams, S K. Wood, P B Wrigglesworth

D.P.H—Margaret Armitstead Horace Bailey, Irene S Bailey, A D Bostock, J R. Brown, A. S Dunn, B R. Ellis, Alexander Gatherer R. E. Jones, William Lees, Joyce E. Leeson, J E. Morris, D W Preston, Rachel D R. Sanem H R. Simpson, D H Vaughan.

University of St. Andrews

On July 1 the following degrees were conferred

M.D—C. C. Booth, J M McKenzie, A P M Forrest (with honours), J O Forfar (with commendation)

Ch.M—W F Walker (with commendation)

M.B Ch.B—F D Lee (with honours), I S Macmillan D N Grant, Ellen C. G Tarvit, Harry Ridehalgh, Gordon Wray, J R. E. Edmondson-Jones (with commendation) J M Anderson, Gerald Asbridge, C W Aven Ann Barber, Beatrice M Caro, Doreen E. Chambers, Hari R Chandrachud A J W Clayton, A R. Cook, Jane M Cowan J N Cross, D J Dallas A G Davies, B O Divis, Gerald Donachie W H. G Douglas, W A A Fajuyigbe, A L Forrest, W R. Grundy Valerie L Gunn, D M Hay M A C. Heavens A H Imrie, Yohannes Kebreth C. D G Lewis, A H McAdam, Rita A McIntyre, G M Maclure W S McMurray, R D Mathias, Eleanor M Mowat, W J Nicol, D W Nisbet, Beryl Y J Pay J L. Penny T T B Phillips, P G C. Robertson Veronica M C. Robinson L C. Rose, Brigid I Russell Natalie A Sender, Avril J Smallwood, J S Souter, J L Stoller, Soad Tabaqchali.

University of Aberdeen

On July 3 the following degrees were conferred

M.D—I R Lawson W G D Murray, C. H Walker

Ch.M—William Burnett (with honours)

M.B, Ch.B—Kathleen M. R. Chrystal J A Baldwin (with honours), G A German D G Jameson (with commendation) Elizabeth A Abernethy J E. Ashun Eileen M Beattie, A. W S Brown R N Carter, Anne M Clunes J T Coull J I Coutts, J A Craig Noreen M Crookshanks Geoffrey Dillon Carol M Edmond, W J W Freeland G A T Gill R. W Glashan D R Grieve E H. Innes, F K. A Laing, J E. Leng, J G Lillie W S P McGregor J S McIntosh Helen R. McKilligan, R M MacLachlan Sheila C. Martin, Catherine K. Masson Moira S Meldrum A P Mowat, A P Nicholson A G Nicol, P P S Nylander, James Proudfoot R L Pyle W D Pyle Jean McC. Ritchie G S Robertson R J Robertson, Isabella M Roe H J M Spicer, G A Taylor, John Taylor R A Tozer, Grace C. Turner, A. C Watt, Jean A Wright, R A Wyper

D.P.H—A G Bearne R F Blackburn, Fiona J Lyall, D M McLellan, Norman Marshall T F Rennie

University of Liverpool

At recent examinations the following were successful

M.D—B J Fairhurst, A W Howel-Evans, E. A Nieman, J R Roberts, D Taylor-Robinson, D J West

Ch.M—E C Edwards, J H Y Fung

M.B, Ch.B—R. Harris, Mary B Jones (with honours), H M Airey, A L Ansdell, W K. H Barnard, J M Beresford, G N Bhadresa, J N Boardman, Mary J Boardman, M J Brindle, A Broughton T N Calvey, R. P Christian, P Cochrane, R. L Coupe, Marie T Cox, D G Ellis, E R Evans, R. E. Fallowfield, R S Ford, W Green, Malvina Harris, J Higham, L. J Hipkin Anne T Irvine, J A Jackson, Anne Jacques, A W Jones, D Jones, E W Jones, K. E. Jones, R H T Jones, J F Kane, W E. Kearns, N B Kirkland, K. Lilley, W F W E. Logan, H Martin, Maureen D Martin, K Martindale, P J Moorhead, Evelyn J Moss, D L Parry, H J Phillips, G H Prince, P G Rae, G B Riley, Catherine O L Rimington, Aline M Robertson R F Robertson, C Roby-Jones, J M Romer, Yvonne A Roope, C. E Sissons, J F Taylor, J M Taylor, R W Taylor, V R. Taylor, N E. Thomas, D E Wallace, R. Whitehead, J G M Williams, J A Wilson, J S Wright, W D R. Winter, C. Wynne.

D.P.H—Sheila I Angles, Cynthia J Bladon, P J Burke. D C. Curtin, A Depares, Cecilia T Diskin, F R. Howell J N Loughlin, Anne D Micah, S Naylor, J M N Packer, J A Seddon, D Wild.

D.M.R.T—A K Bose, G A L. G Glazebrook, R. Spencer

D.M.R.D—Varunee Amatyakul, E. H Burrows, L R. Levin T Nopparat, R. G Pitman, H G Row

University of Sheffield

Mr A. W. Kay, lecturer in surgery in the University of Glasgow, has been appointed to the chair of surgery in succession to Prof R. P Jepson.

Mr Kay, who is 41 years of age, graduated M.B with honours from the University of Glasgow in 1939 After holding house-appointments in Glasgow at the Western Infirmary and the Royal Hospital for Sick Children, he was appointed in 1941 a Hall tutorial fellow and clinical assistant at the Western Infirmary In 1942 he took the F.R.C.S.E. and in 1944 he received the degree of M.D with honours and was awarded the Bellahouston medal. In 1945 he was appointed assistant in the department of surgery at Glasgow University and surgeon to outpatients at the Western Infirmary After two years as a major in the R.A.M C., when he was in charge of the surgical division at Millbank Military Hospital, he returned to Glasgow as consultant surgeon to the Western Infirmary and honorary lecturer in surgery at the university In 1949 he took the CH.M. with honours In 1955 he became first assistant to Prof. C. F W Illingworth, and he was appointed to his present lectureship in 1956 He has also been surgeon in charge of wards at the Western Infirmary since 1956 He is a member of the Medical Research Council's external scientific staff. He was elected F.R.F.P.S in 1956. Mr Kay is co-author of a textbook of surgical physiology which is in the press, and his published work includes a paper on the augmented histamine test.

University of Glasgow

On July 5 the following degrees were confered

M.D—W S Foulds, W J Gordon, R. M H McMinn, J T Nasmith, D D Smith H I Tankel (with commendation), E. McL Barbour, J M Crawford, J A McKinnon

M.B, Ch.B—Alastair Ballantyne, J H H. Bowie, Margaret C. Donnelly, J M Howat P H Pinkerton, R. L Robinson J P Studzinski J K Todd Frederick Walker (with commendation), Oladele da Rocha Afodu, Ahmed Nawaz Ahmad, W C. Alston, G K. K. Asamoah H D Baillie, Robert Baird, Maureen E Barr, R. F Barr Isabelle B Barrie, W N Baxter B J Beadsworth, John Behnar, Dorothy A Brown, Jean G Brownlie, K. D Buchanan, Hellen S Conn, W G Conn, N A Coutts J E N Dickie, Archibald Downie, Bryan Drever J C. Drever, Macadam Duncan J J Dunn, J A C Fisher, Adam Fleck, Stewart Fletcher, John Fyfe Catherine A Gardner, Joyce O Garven R T Glen, Robert Gordon, John Gray, K. D Griffin, Margaret E. Hanlon, W J Haran, C D Hardie H C Hendrie, Margaret Hennigan D M C. Hislop, Margaret A Hodson, I M Hynd G M Irvine, J F St Clair, Irene M J Jackson J C Kellock, M A Kelly, Martin Kelvin, Margaret M Kennedy, H A Kilpatrick, I McA Kyles, Marjorie M Langmuir, J P Lanz, I McA Ledingham, R. E M Lees, D R H Lewis T I McBride, J P McConnell, D M MacDermid D M. Macfadyen, D B MacGregor Eileen McGuire, R. L McKechnie M C. MacKenzie, C. A MacLean, Norman MacLean R B Macleod, G W McNicol Margaret M Macpherson, J M Maguire, J P Malone, W D Martin, Heather M May, J M B May, Marie H H Mitchell, John Moffat, Jack Murgatroyd, Helen McB G Murray Jean R. Nairn E. A Neville Elizabeth J Newson, V R Nurse S S I Parker, K. C. Paton Mary H Paul Andrew Pollock J G Pollock Janet S Primrose, A J Quigley, A A Reid, Daniel Reid, G L I Reilly Elizabeth M Riddell, Anthony Rourke, Elizabeth M. Russell, J L Russell Robert Scott, W S Scott M S Selzer M G Sharman G R Sharp, William Simpson, J F Smart, Donald Smith Khodayar Soroushian, J C. Spence, A R. Stewart, T McC. Stewart, W B Stewart, Sheila M Strachan, M C. Thomson J K. Todd, Marion Vallance, Alan Vest, Evelyn McD Walker, J P Wall J M Walsh, R A Willett, Maureen L Wyllie H N Young

University of Dublin

On July 3 at Trinity College, Dublin, the following degrees were conferred

M.B, B.Ch. B.A.O—Sara R Abels, Bridget M Acheson, H B Allen, John Bennett P J Blackburn J S Brown R. J M Collis, Edith M Cross, N J B De Wet Bridget A M Dunne Michael Elder Brian Gallagher, P B Galvin, H G Grace Sheila D Graham D E Jones Anne Llewellyn, S H M Logan Patricia M Norman, John Quinn, Joan Richards, Annette L K. Roberts, P J Robinson W M Robinson Leona J Rust Pauline E. Tan, D G Weir, T D H Wilson, Theodore Winston Susan E. J Young

M.D—T H Bewley, F O Dosekun, Edna La C. Murphy

M.A.O—C. J B Orr

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[1] See *Lancet*, 1958, i 1376

Royal College of Surgeons of England

On July 3, Mr Eric Riches and Sir Arthur Porritt were re-elected, and Mr. F W Holdsworth and Mr J Cridlan Barrett were elected members of the council

Order of St. John of Jerusalem

The Queen has sanctioned the following promotions in, and appointments to, this order

As Knights —Colonel F A Bearn, C B E, D S O, M C, M D, H S Taylor-Young, F R C S

As Commanders —Major-General A E Campbell, C B, M D, Q H P, Colonel Malcolm MacEwan, D S O, O B E, D F C, T D, M B, Surgeon Rear-Admiral D M Beaton, O B E, L R C P E, Q H P, Surgeon Rear Admiral D F Walsh, O B E, F R C S E, E C Brewis, M D, T W A Gray, M D, Colonel G E Wight, O B E, M D, Elsie C Hanson, M D

As Officers —Major-General T F M Woods, O B E, M D, Q H P, Lieut-Colonel D H D Burbridge, M R C S, J B Dobson, F R C S, A D Griffith, L M S S A, Archibald Russell, M B, D P Kennedy, E D, M B, J G Stewart, M C, M B, T H Pullar, M R C P, James Moffat, M B, W A Hogg, M B, H J Hoby, M R C S, L S Potter, M B, Colonel Geoffrey Anderton, O B E, M B, F L Fletcher, M R C P, J W Pickles, M B, C D Short, M D, Brigadier C S Thompson, O B E, M D, M G Townsend, M D, Marguerite F E Wylie, M R C S

Society of Apothecaries of London

On July 22, at 8 30 P M at the hall of this society, Black Friars Lane, E C 4, the Master will confer the honorary freedom of the society on Sir Henry Souttar and bestow the Galen medal on Sir Macfarlane Burnet

Royal Society of Medicine

The following officers have been elected for 1958–59

President, Sir Geoffrey Marshall, immediate past president, Sir Clement Price Thomas, hon treasurers, Mr E G Muir and Dr Basil Kiernander, hon secretaries, Mr Terence Cawthorne and Prof R H S Thompson, hon librarians, Prof C G Rob and Dr J S Richardson, hon editors, Dr E C Warner and Mr Selwyn Taylor, hon directors of photography, Mr Myles Formby and Dr F C Kelly

Institute of Diseases of the Chest, London

Clinical demonstrations, open to doctors without fee, will be continued at this institute (in the grounds of the Brompton Hospital, Fulham Road, S W 3) on Fridays at 5 P M throughout the summer

Royal Society

With awards from the society's Nuffield Foundation Commonwealth bursaries scheme, Prof T Gilman (Natal) is to study skin regeneration at University College, London, and Dr T B Teoh (Hong Kong) bile thrombi at University College Hospital Medical School

Royal Medical Benevolent Fund

The annual general meeting of this Fund is to be held on Wednesday, July 30, at 5 P M at 11, Chandos Street, London, W 1

Anglo-French Bursaries

Awards have been made for work in France in 1958 under the exchange arranged by the Institut National d'Hygiène, Paris, and the Ciba Foundation, London, to Dr Evan Fletcher, Dr J G Howard, Dr E M Jepson, Mr J F O Mitchell, and Dr P M Peacock

Harveian Society of London

Members of this society on June 22 attended a service at Hempstead Church, Essex, where William Harvey is buried Lessons were read by Dr D A Imrie, president of the society, and Mr A Dickson Wright, president of the Harvey Tercentenary Congress, and the Bishop of Colchester preached the sermon The appeal fund for restoration of the church tower has now reached over £3000

International Congress of Psychotherapy

This congress will be held in Barcelona from Sept 1 to 7 Application to take part should be made to the secretary, Catedra de Psiquiatria de la Facultad de Medicina, Casanova 143, Barcelona There will be a special section on psychopharmacology, details of which may be had from Prof F G Valdecasas, department of pharmacology of the faculty Applications must be submitted not later than July 31

British Association of Paediatric Surgeons

This association will hold its annual meeting in London from *Wednesday, July 23, to Friday, July 25*

International Congress on Nutrition

This congress will be held in Washington from Sept 1 to 7, 1960 Further particulars may be had from Dr M O Lee 9650, Wisconsin Avenue, Washington 14, D C, U S A

Health Services Whitley Council

The council have appointed Sir William Matthews, a forme under-secretary at the Treasury, and Mr R E Peers, assistan secretary of King Edward's Hospital Fund for London, to joi Sir Noel Hall *on a committee to compare the wages of Nationa* Health Service workers with those of people in similar employment

Changes in the Prescribed Diseases Schedule

The Minister of Pensions and National Insurance has made regulations (S I 1958, no 1068) altering the schedule of occupational diseases for which workers are covered for the benefits of the Industrial Injuries Act The regulations implement the recent recommendations of the Industrial Injuries Advisory Council (see *Lancet*, 1958, i, 906)

Progress in the Biological Sciences in Relation to Dermatology

A course on this subject will be held by the University of Cambridge Postgraduate Medical School from Sept 22 to 27

It will consist of half-day sessions, each devoted to a group of papers on the same or related subjects, including the melanocyte and melanogenesis, cutaneous innervation, the histochemical investigation of the skin, bacteriology, psychophysiological mechanisms, comparative medicine, immunology, inflammation, carcinogenesis, radiation of the skin, and pharmacology The course is designed for dermatologists but is open to any doctor interested in the subjects under discussion Accommodation and board will be provided in Downing College Further particulars may be had from the secretary of the Medical School, Tennis Court Road, Cambridge

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On July 3 at the Middlesex Hospital Medical School Lord Astor of Hever presented the Comfort Crookshank medal to Prof Charles Huggins of Chicago

List of Films on Human Anatomy and Embryology —In preparing the second edition of this world list Dr R Brouwer has found it necessary to limit the number of films selected Some films showing the anatomy or embryology of animals have been omitted, but others *dealing with human anatomy* and embryology have been added Copies (£1) are available from the Netherlands Scientific Film Association, Catharijnesingel 59, Ingang Sterrenbos, *Utrecht*, Holland

Diary of the Week

JULY 13 TO 19

Monday, 14th

GUY'S HOSPITAL MEDICAL SCHOOL, London Bridge, S E 1
5 P M Prof Alfred Jost Biological Basis of Some Recent Concepts about Sex (Addison lecture)

Tuesday, 15th

UNIVERSITY OF LONDON
5 P M (St Thomas's Hospital Medical School, S E 1) Dr Frank Gerbode (San Francisco) Aspects of Intracardiac Surgery

BRITISH MEDICAL ASSOCIATION
3 P M *With the Association of Industrial Medical Officers* (Portland Building, Nottingham University) Dr Andrew Meiklejohn Industrial Health—Meeting the Challenge (Mackenzie Industrial Health lecture)

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, 18, Nicolson Street, Edinburgh, 8
3 30 P M Prof I S Ravdin (Philadelphia) Recent Advances in Blood-transfusion

Wednesday, 16th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
2 P M Dr A C Cunliffe Cutaneous Hypersensitivity

Friday, 18th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields W C 2
4 P M Prof H G Radden Local Factors in Healing of the Alveolar Tissues (Charles Tomes lecture)

The Lancet · Saturday 19 July 1958

PROGRESS IN THE CONTROL AND REDUCTION OF LEPROSY

Sir Leonard Rogers
K.C.S.I., M.D. Lond., LL.D. Glasg., F.R.C.P., F.R.C.S., F.R.S.

As the result of several years' research in Calcutta, I was able to record in 1917 that a number of fairly early cases of leprosy had been cleared of active symptoms by injection of a new soluble hydnocarpate of soda, which replaced the ineffective and nauseating oral administration of chaulmoogra oils (Rogers 1918). Up to that time the only plan in common use for controlling leprosy was the centuries-old compulsory segregation for life of all discovered cases. This drastic measure—unknown in modern times in the case of any other such chronic disease—had failed repeatedly to achieve its avowed purpose.

After my retirement from India I devoted three years to a comprehensive study of the previous fifty years' literature of leprosy (Rogers 1922) and formulated a plan of control (Rogers and Muir 1925–46).

Principles

Compulsory segregation failed because it led to the hiding of patients in South Africa and the Philippines, where it was most rigidly enforced, cases were not notified until seven to nine years after the first appearance of symptoms. During this time of hiding they had infected members of their households and other close contacts, who carried on the disease indefinitely.

Moreover I obtained evidence that only a fifth to a fourth of all the cases were highly infectious—namely, the mucocutaneous type (to use the old but more descriptive term rather than the indefinite "lepromatous", which has come into use). Their infectivity is due to their sneezing and coughing myriads of lepra bacilli from their infected mucous membranes over highly susceptible and lightly clothed children of their households in humid, hot, insect-infested regions which constitute nearly all the areas of high incidence of leprosy (Rogers 1923). As the earliest symptoms of leprosy are found on exposed parts of the body, punctures of the skin by insects and abrasions afford entry for the bacilli, although the evidence is against direct inoculation by contaminated insects.

For these and other reasons I laid down the following principles of prophylaxis, which were adopted by the British Leprosy Relief Association (BELRA) shortly after its foundation in 1924, and have ever since been advocated by it.

(1) *Surveys of people in samples of leprosy-infected countries to determine extent of leprosy.*—The necessity for this measure is clearly shown by the fact that in India Muir found the true number of cases to be eight times the official ten-yearly census figures. A similar survey revealed the very unexpected number of 400,000 cases in Nigeria and 254,000 in British East Africa (Rogers 1955).

(2) *Only highly infectious mucocutaneous cases are in urgent need of isolation to stop new infections.*—The economic importance of this principle will be clear from the experience of South Africa (Rogers and Muir 1946, Rogers 1954). In that country segregation for life of all discovered leprosy patients has been enforced since 1892 without even preventing a steady increase of the disease due to hiding of the cases to avoid lifelong imprisonment without hope of successful treatment. But, when the value of hydnocarpate injections in early cases became known, patients in the early stages flocked voluntarily into the leprosarium for treatment. The medical authorities thought it necessary to continue compulsory segregation for all active cases because the disease was scattered over an immense area, but patients without active symptoms, chiefly with chronic neural leprosy, were released. The average duration of symptoms on admission fell from seven to two or three years, and the incidence of leprosy fell from 2.21 to 0.77 per 1000 by 1953. This notable success was obtained at a cost in some years of £250,000, or £100 per patient per annum; this only a gold-producing country could afford. But the accompanying table shows that over 700,000 cases require treatment in British tropical African territories compared to an average of less than 2500 under segregation in South Africa.

(3) *Voluntary isolation of all infective patients in special villages at very low cost.*—Soon after BELRA was founded, Lord Lugard, formerly Governor of Nigeria, told me that in South-East Nigeria it had been customary to isolate advanced cases of leprosy in special villages in which no uninfected people were allowed to reside. I therefore decided to revive this custom as the only economical plan of isolating the highly infective cases. This was later borne out by surveys revealing an estimate of 177,722 unisolated infective cases in British tropical African territories. Yet the recently constructed leprosarium in East Africa, with an attached research laboratory, cost BELRA alone £27,000 in capital and £4000 annually in upkeep.

(4) *Three-yearly surveys of contacts to detect newly developing cases in earliest easily curable stage.*—The necessity for this additional—and, I believe, previously unused—precaution may be illustrated by T. F. Davey's statement to me that on the third such survey of a tribe 7000 strong in South-East Nigeria, although not a single infective case was found, no less than 40 persons were discovered with very early symptoms which had appeared since the last survey. Such cases can now quickly be cleared up whereas formerly they would have become infective—probably long before they were segregated.

Trials of New Plan of Reducing Leprosy Incidence

Small-scale Trial in Nauru Island, Australia, in 1925

After consulting me, the Australian medical authorities made a survey of the small indigenous population of Nauru and found that nearly 30% showed signs of leprosy. Of the patients thus discovered, 90% were in a very early stage of the disease, but there were also some highly infectious cases. My plan was put into operation, and three years later Bray (1930) reported that the number of cases had been reduced by 40%. In 1934 Grant recorded a reduction by 66%. Moreover scarcely any of the early cases had gone on to reach an infective stage. Eighteen years later Wade and Ledowsky (1952) found only a seventh of the earlier numbers. The latest report, in 1957, shows only 47 cases, or 2.8 per 1000, of whom only 9 were isolated as infective.

INCIDENCE AND CONTROL OF LEPROSY IN BRITISH TROPICAL AFRICAN TERRITORIES

Territory	Known and estimated total cases						Infective cases				
	Population	Known cases under treatment	Estimated unknown and untreated cases	Total of known and estimated cases	Total cases per 1000 of population	Percentage of total cases under treatment	Infective cases isolated and treated	Infective cases unisolated and untreated	Total known and estimated infective cases	Percentage of infective cases isolated and treated	Estimated yearly cases infected from unisolated cases
Eastern Nigeria	8,000,000	28,237	54,000	82,237	10 3	34 3	15,572	5428	21,000	74 2	1084
Western Nigeria	6,000,000	8268	61,000	69,245	11 5	11 9	5242	12,058	17,300	30 3	2411
Northern Nigeria	16,800,000	17,266	250,000	267,266	15 9	6 5	11,310	55,390	66,700	17 0	11,078
East Africa	15,272,784	16,446	203,450	219,890	14 4	7 5	11,666	92,734	104,400	11 2	18,572
Gold Coast	5,000,000	14,860	50,000	64,860	13 0	22 9	860	12,112	12,972	6 6	2422
Total	51,072,784	85,077	618,450	703,498	13 8	12 1	44,650	177,722	222,372	20 0	35,567

Control Measures in Hyperendemic Areas of Tropical Africa

In 1923 I published a map of the world to show that nearly all the highest incidences of leprosy are met with in hot humid tropical and subtropical climates with annual rainfalls of 30–60 in or more, especially in Africa, where later surveys showed that 86% of the leprosy patients for whom the British are responsible are found This led **Belra** to concentrate its main efforts on that hyperendemic region

Progress in the control of leprosy in the British Commonwealth has been recorded (Rogers 1954, 1955), and the present position in tropical Africa is illustrated by the comprehensive data in the accompanying table

The estimated yearly new infections from unisolated cases were estimated at a yearly rate of one child for every five highly infective cases in their households This I regard as a conservative estimate in view of the fact that early cases are nearly always found in households containing an active mucocutaneous case

The table shows that the rates per 1000 population vary between 10 3 and 15 9 in British tropical African areas Yet those of 96 countries I worked out for three editions of *Leprosy* (Rogers and Muir 1925–1946) and later unrecorded ones show no such high incidence in extensive areas with high populations For example, India in 1941 showed a rate of only 3 4 in spite of the number of cases having been estimated by surveys at eight times the census figure

Nigeria presents the greatest leprosy problem in the world, with an estimate of 418,748 cases (see table) East African areas come a good second, with 219,890 in Uganda, Tanganyika, and Nyasaland, apart from Kenya, where suitable data are not available The Gold Coast has an estimated number of 64,860 cases, making a grand total of 703,498 in the areas under consideration—about three-quarters of the probable total cases in British territories all over the world, after allowance has been made for underestimates in those of them which have not yet made surveys to determine the true numbers (Rogers 1954)

Belra has concentrated on control measures of different degree according to local facilities as the most urgent task, beginning first in Eastern Nigeria, where alone it has maintained them long enough to produce material results, but also to a less extent in Western Nigeria, and only for the last few years in Northern Nigeria

East Africa presents a difficult problem because the cases are scattered over a million square miles of territory It was found advisable to contribute largely toward the cost of construction of a large leprosarium for 1000 infective cases, with a research laboratory

In the Gold Coast it is only quite recently that vigorous efforts have been made to supply treatment to as many cases as possible at clinics situated at intervals of 10–15 miles along all the main and most of the subsidiary roads by a staff on bicycles over a territory of 91,000 square miles—all until recently under control of a single medical officer, Dr A Mackelvie By this means 14,860 cases, or about 23% of the total estimated cases, are receiving regular treatment and many of them prevented from developing into a highly infectious stage

That experience emphasises the importance of supplying a whole-time officer to take charge of leprosy-relief measures in any extensively infected area **Belra** has several times initiated such measures by offering to find half the salary of such a specialist medical man for a term of years

Returning to the data of the three divisions of Nigeria we find that the progress made in the proportion of cases under treatment and the proportion of infective cases isolated and treated, and consequently the degree of control supplied, increases with the length of time during which the control measures have been applied Thus the figures are highest (34 3% and 74 2% respectively) in Eastern Nigeria and lowest (6 5% and 17 0% respectively) in the Northern Division Western Nigeria shows intermediate figures (11 5% and 30 3% respectively) but has the second highest figure of the whole table of infective cases isolated and treated We must therefore turn to the work in Eastern Nigeria for evidence of any material reduction of the incidence of leprosy due to the modern measures of control

Evidence of Material Reduction of Leprosy Incidence in Eastern Nigeria within Two Decades

When, as a result of the success of the small-scale leprosy-control measures in Nauru Island (see above) it was decided to conduct a large-scale trial in the Eastern Nigerian hyperendemic area, it was fortunate that the help of two successive medical missionaries was available The economical village system of isolation was first introduced for the isolation and treatment of infective cases by J A Kinnear Brown (personal communication) His health broke down—although subsequently he was able to start the same measure in Uganda, and he was succeeded by T F Davey, who made careful surveys of all the people in different groups and repeated such surveys from time to time Only a brief summary of his results (Davey et al 1956) can be given here

No less than 302 special isolation villages were constructed, "often at negligible cost and with the cooperation of the entire community" In one instance repeated surveys disclosed a reduction of leprosy from 31 to only 5 per 1000 in the eight years 1943–51 In another clan the disease almost completely died out within ten years Many patients with tuberculoid leprosy were discharged in an inactive condition, but lepromatous cases rarely cleared up and then only slowly Unstable "indeterminate" cases treated with hydnocarpus oil rarely degenerated into lepromatous leprosy Through its action on such patients in particular hydnocarpus oil must have contributed to the decline of leprosy In this and contemporary trials striking results were recorded before sulphones became the standard treatment in Eastern Nigeria in 1951 in the form of oral dapsone Davey et al (1956) record that during the past six years a mass of evidence has accumulated of a decline in the incidence of the disease that is widespread and it is gaining in momentum each year Thus, whereas in three provinces 30,630 patients with active leprosy were receiving treatment in December, 1948, by the end of 1954 the number had dropped to 14,770, a decline of 50% Davey et al discuss other possible causes of the great decline and conclude that they could have produced no such profound effects in the space of seven years Moreover, during the last fifteen years about 30,000 patients, including most of the infective ones, have been isolated for longer or shorter periods in local segregation villages Evidently the intense and widespread work for the control of leprosy has been of great importance in Eastern Nigeria

Present Position of Sulphone Treatment of Leprosy

The discovery (by American leprologists at the Carville leprosarium in Louisiana) that sulphones are efficacious against leprosy is undoubtedly the greatest advance in the history of the disease Lowe (1950), working for BELRA in Eastern Nigeria, was able to demonstrate the value of oral administration of the more economical mother sulphone dapsone, which could be used more easily on a large scale The most important property of the sulphones is their effect in healing the lesions of the nose, throat, and larynx, and ulcerating nodes, and very greatly reducing their infectivity

There remains the serious difficulty of getting rid of the immense numbers of lepra bacilli in the nodules Sweetes (1955) records that, after three years' sulphone treatment of 800 lepromatous cases, in only 11% had the patient's tissues been freed from the bacilli American leprologists therefore think it necessary to continue the treatment of such cases for years at great total cost

Personally I very much doubt whether the comparatively few bacilli remaining deeply situated in subcutaneous nodules are likely to escape from the body in numbers constituting any material danger to other people I therefore advise that, whenever numerous untreated and far more highly infectious cases are awaiting isolation, nearly cleared patients should be discharged from isolation to attend clinics and be bacteriologically examined from time to time for signs of relapse

Further research for active drugs to supplement the sulphones is needed and is being pursued Thus BELRA has originated and is financing such work in both West and East Africa Any advances that may be made will bring nearer the day when leprosy will be virtually eliminated from the worst-infected areas of the world, by the measures so long advocated by me and now proved effective in the hyperendemic region of Eastern Nigeria

Summary and Conclusions

A plan formulated in the 1920s for reducing the incidence of leprosy proved highly successful on a small scale in the island of Nauru

The British Leprosy Relief Association, founded in 1924, helped to finance during two decades a large-scale trial of the new methods in highly infected Eastern Nigeria As a result the incidence of leprosy there was materially reduced

In the 1940s American leprologists discovered a new and potent remedy (especially in infective mucocutaneous, or lepromatous leprosy) in the sulphones By the beginning of the present decade further researches in Nigeria had led to the simple and effective use orally of the mother sulphone, now known as dapsone

Recent surveys in British tropical African territories have produced the estimated figure of 703,498 cases of leprosy, of which 85,000 (12%) are being treated in several hundred outpatient clinics, and 44,656 highly infective cases are isolated with treatment in three hundred special villages constructed for them at very low cost compared with large segregation settlements Moreover, some promising new drugs have been tested in the research laboratories of West and East Africa to supplement the sulphones

The way has thus been prepared for the steady reduction in the incidence of the ancient scourge of leprosy, probably nearly to the point of eradication—if only the essential additional staff and funds are forthcoming

REFERENCES

Bray, G W (1930) *Proc R Soc Med* 23, 26
Davey, T F, Ross, C M, Nicholson, B (1956) *Brit med J* ii, 65
Grant, A M B (1934) *Int J Leprosy*, 2, 305
Lowe, J (1950) *Lancet*, i, 145
Rogers, L (1918) *Indian J med Res* 5, 277
— (1922) *Brit med J* i, 987
— (1923) *Trans R Soc trop Med Hyg* 6, 440
— (1954) *Trans R Soc Arts*, p 987
— (1955) *Lancet*, ii, 80
— Muir, E (1946) Leprosy, 3rd ed. Bristol
Sweetes, L. (1955) *Ann Soc belge Méd trop* 35, 758
Wade, W W, Ledowsky, V (1952) *Int J Leprosy*, 20, 1

INCIDENCE, ÆTIOLOGY, AND PREVENTION OF HEAT ILLNESS ON SHIPS IN THE PERSIAN GULF

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THE fabulously rich State of Kuwait exported some 56 million tons of oil last year There is promise of a higher annual yield Already, however, 230–240 tankers (and 14,000 or so sailors) call *each month* at Kuwait's Mina-al-Ahmadi (fig 1) to load oil for world markets In June, July, August, and September of each year this operation is carried out in environmental shade temperatures of 95–120°F (35–49°C) dry-bulb and 60–90°F (15–32°C) wet-bulb Midsummer sun temperatures may exceed 160°F (71°C) In such circumstances the occurrence of heat casualties is not surprising

The crews of ships sailing in the Red Sea, Gulf of Aden, and Persian Gulf have never been exempt from the effects of heat Cases aboard Naval vessels in these and neighbouring waters have been described in recent years by McLean (1943), Stenning (1945), Thomson (1946) and Crowden (1951) Ellis (1955) considered that unreported heat effects had a serious impact upon the Fleet during the second world war

We report here 128 cases of heat illness arising in the summer months of 1956 and 1957 among personnel of

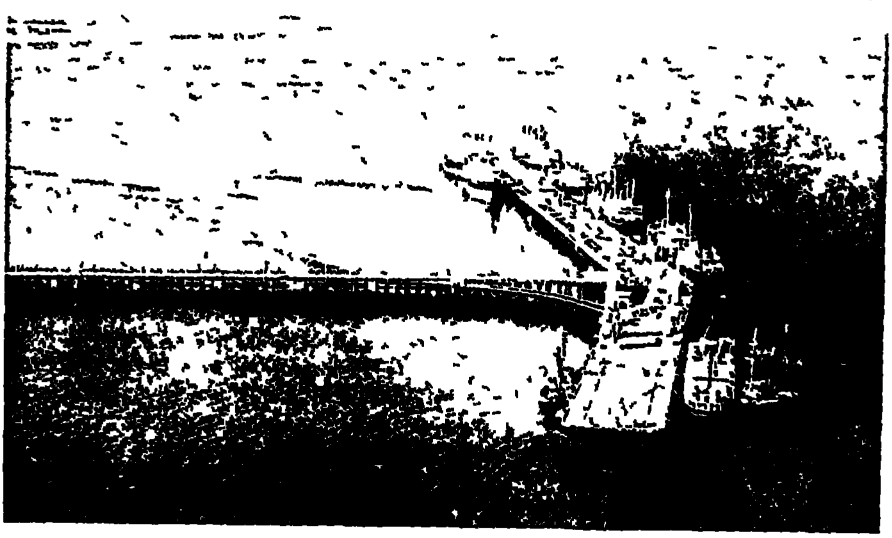

Fig 1—Oil pier, Mina-al-Ahmadi

oil-tankers sailing in the Persian Gulf and calling at Mina-al-Ahmadi

Patients and Methods

The pier at Mina-al-Ahmadi is provided with a clinic and heatstroke treatment room where the patients were first seen by the duty quarantine medical officer (Kuwait State health department) For further investigation and treatment, some patients were admitted to the Kuwait Oil Company hospital at Magwa, 15 miles inland

Clinical impressions were augmented by estimations of chloride content of urine, whole blood, and plasma, sodium and potassium levels of whole blood and plasma, blood-urea level, and plasma specific gravity (methods after King 1951) Urine samples were first screened by the Fantus (1936) technique, and urine found to contain less than 3 g of chloride per litre was further examined by the Volhard titration method

The investigations were supported by a survey of acclimatisation and health of British, American, Arab, and Indian residents ashore, in the Kuwait Oil Company town of Ahmadi

Environmental temperatures—e g, in ship compartments—were measured with a sling hygrometer, and air movement with a katathermometer Coastal temperatures in fig 2 were derived from the Kuwait Oil Company marine department's meteorology station at Mina-al-Ahmadi, where the thermometers were mounted in a Stevenson screen

Incidence

During the survey periods, June-September, 1956 and 1957, 1807 tankers berthed at Mina-al-Ahmadi, representing at most 108,000 seamen Of those who required or sought medical attention on the pier, 128 were found to be suffering from the effects of heat From these figures an approximate incidence index of 1 in 850 may be derived, but this is possibly not a true picture of the overall incidence of heat illness on ships in the Persian Gulf, we have no accurate information of the numbers seen and treated at other oil ports on the Gulf—e g, at Abadan, Umm Said, or Dhahran

TABLE I—CLASSIFICATION OF 128 CASES

Syndrome	No of cases
Heatstroke	2
Heat hyperpyrexia	1
Borderline heat hyperpyrexia	5
Heat exhaustion syndromes	
(1) severe	
Salt deficiency, with or without *heat cramps*	59
Anhidrotic heat exhaustion	1
Primary water deficiency	0
(2) mild	
Exercise-induced heat collapse, heat syncope, mild water deficiency, acute heat neurasthenia	60

Classification

Local physicians divide heat illness into three groups—mild heat exhaustion, severe heat exhaustion, and heat hyperpyrexia (including heatstroke) Abundant clinical experience of heat effects, coupled with heavy outpatient sessions, makes further categorisation by laboratory investigation largely unnecessary and impracticable In table I this simple division is correlated as far as possible with classification of the 128 cases according to the most recent proposals of the *Medical* Research Council's Climatic Physiology Subcommittee for nomenclature and coding of heat-illness (Weiner and Horne 1958)

Severe primary water-deficiency heat exhaustion, such as may occur in men lost in the desert, was not seen among the tanker personnel Prickly heat and other skin disease referable to high environmental temperatures are not included in this table

Clinical Observations

Complete absence of sweating and a rise in body temperature above an arbitrary level of 106°F (41°C) constitute *heat hyperpyrexia*—in the presence of environmental heat stress and the absence of any other cause of the pyrexia If in addition the patient has coma, convulsion, or delirium, the condition is by common consent described as *heatstroke* Choice of the arbitrary figure 106°F is unsatisfactory, and heatstroke with a body temperature of 105°F (40 5°C) is described in two cases by Leithead and Wilkinson (1958)

Of the 3 patients listed here, 1 was conscious but irrational with a body temperature of 106°F (41°C) and the other 2—British youths aged 22 and 24—had shown coma and convulsions with temperatures noted by intelligent lay observers to be 110°F (43 3°C) and 108°F (42 2°C) respectively The issue in these two cases had been decided on board ship, before they reached medical attention one recovered (without any apparent residual damage to the central nervous system) after being promptly put in the meat-storage space (the only " cool " compartment of this particular ship), and the other aspirated vomitus and died during correct treatment by applications of chilled water to the body and vigorous fanning to provide air movement

Theoretically, it is inadvisable to apply ice chips or ice-cold water in these cases, because one may induce vasoconstriction which will prevent the blood from circulating through the cooled skin But the successful use of a refrigerator by a resourceful ship's captain illustrates the fact that in practice advantage should be taken of any available cooling device

In 5 patients the body temperature lay between 103° nd 106°F (39 5–41°C) All were conscious and rational, nd have been listed here as cases of *borderline heat perpyrexia*, a term used by Ladell et al (1944) Of adell's 12 patients, 10 had anhidrosis when examined, hereas all our 5 were sweating Urinary chloride excre-on (Volhard technique) ranged from 3 to 11 g per litre, nd, in the 3 cases in which they were estimated, whole-lood and plasma levels of sodium, potassium, and hloride were within normal limits

Anhidrotic heat exhaustion (thermogenic anhidrosis, opical anhidrotic asthenia, heat exhaustion type II) as escribed by Wolkin et al (1944), Allen and O'Brien 1944), and Ladell et al (1944) was encountered only nce. Horne and Mole (1950) and O'Brien (1948) have hown that four to seven months' exposure to a hot cli-nate is usual before onset of this syndrome, and when ney arrived at Mina-al-Ahmadi European tanker crews ad seldom been exposed to heat stress for more than n to fourteen days

The patient listed here was an Indian, aged 36, who had ravelled by passenger ship from Bombay to join an oil-anker in the Persian Gulf He was found to have extensive rickly heat with large areas of miliaria profunda and anhi-rosis on the trunk, his temperature was 102 F (39°C), he had achycardia and hyperpnœa, and he was sweating only on the ace, hands, feet, and perineum His urine contained 3 g odium chloride per litre

Shortly after Sargent and Slutsky (1957), from a com-rehensive review of the eccrine miliarias, concluded that natives of India are free from this syndrome, Jelliffe 1958) described it in Bengali children

Our 59 cases of *salt-deficiency heat exhaustion* have been lescribed in detail elsewhere (Leithead et al 1958) They were distinguished from other exhaustion syn-lromes by the absence (or near absence) of urinary odium chloride, with reduction of blood-chloride in cases thus investigated Muscle cramps (heat cramps, miners' cramps stokers' cramps) were noted in 60% of these patients, not in any of the other groups No clini-cal purpose is served, we think, by separate classification of cramps, which are now believed to be directly caused by salt deficiency

Unless there are muscle cramps, or the chloride levels of blood and urine are known, salt-deficiency heat exhaustion is not readily distinguishable from such conditions as exercise-induced heat collapse or acute heat neurasthenia Generally, however, it is a more severe illness, culminating eventually in oligæmic shock, and most patients need several days' salt and water replacement and rest 3 typical cases in this series required an average of 40 g of salt by mouth before clinical improvement and the reappearance of urinary chloride in significant quantities (i e , above 1 g NaCl per litre)

Heat collapse (Dreosti 1937 and Weiner 1938) and *heat syncope* are allied circulatory disorders Weiner observed syncope in Bantu miners who remained erect after exercise in a hot humid environment (wet-bulb temperature 94–95 F, or 35 C) In unacclimatised immigrants, during their first few days in a hot climate, sudden postural change may cause giddiness and even syncope These disorders are attributed to extensive vasodilatation by direct action of heat, consequent " pooling " of the blood in the lower half of the body, postural hypotension, and hence inadequacy in the supply of blood to the brain. Giddiness, exhaustion, and headache are vague symptoms referable also to mild water deficiency, to acute heat neurasthenia, and to early salt depletion, and unfortunately they parallel the type of complaints chosen by malingerers As operators of tanker fleets naturally aim at a quick turnround of their ships in port, close investigation and differentiation of patients with such mild symptoms was impossible Our practice was therefore limited to separating the severe from the mild cases, but we can say that, though salt deficiency was found in a few patients with mild symptoms, it was invariably present in all severe exhaustion cases Caplan (1943) also found low plasma-chlorides more frequently in clinically severe heat exhaustion

Prickly heat was noted in 25% of all cases, and—except in the single case of anhidrotic heat exhaustion—it bore no apparent relation to the type of heat illness No attempt was made to estimate its incidence in tanker personnel, but analyses by Smith (1957) of sickness returns for Naval vessels in the Persian Gulf in 1948–52 showed an incidence of skin disease (unqualified, but including prickly heat) of about 4%

Ætiological Factors

Environmental Temperatures

To within 7–10 miles of the coast, Kuwait has a desert climate, but beside the sea the air is more humid, and readings taken at the shore end of the pier at Mina-al-Ahmadi reflect the climate experienced in the Red Sea and Persian Gulf These readings are charted in fig 2, along with saturation deficiencies and monthly incidence of marine heat illness for the survey periods It is evident that, at high ambient temperatures, a sustained drop in saturation deficiency is associated with an increase in the amount of heat illness among tanker crews This is mainly due to decreased evaporation of sweat and therefore decreased loss of heat in people whose acclimatisation is insufficient to take the extra heat load Ashore in Kuwait the local physicians recognise that humid spells are liable

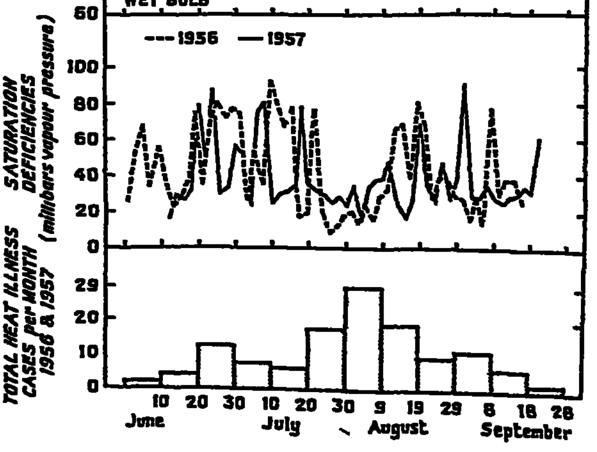

Fig 2—Incidence of heat illness in relation to shade temperature (3 p.m) and humidity readings during summer in Kuwait coastal area. Interrupted lines, 1956 Continuous lines, 1957

to cause heat syncope and collapse among previously healthy immigrant (non-European) workers

Geographical

Heat casualties arise whenever environmental heat stress exceeds the level which is critical for the person concerned They may therefore be encountered far from the tropics—e g, in boiler rooms or coalmines Cases of heatstroke in Britain recently reported by Harris and Hutton (1956) and Stoddart (1958) occurred in an operating-theatre and a Turkish bath

But, although the geographical distribution is wide (Shattuck and Hilferty 1936), we may note that heat illness has always been a feature of Arabia and the Middle East (Friend 1932) By virtue of their poor acclimatisation, arduous duties, heavy equipment, and often unsuitable clothing, Western armies have suffered considerably in Middle Eastern areas "The heat, and the fever" killed members of the Crusade of Edward I (Lindsay 1936) Among British Expeditionary Forces in Mesopotamia during the first world War, there were in one month no fewer than 425 deaths from heatstroke (Willcox 1920), but this harrowing experience of Willcox, and of Hearne (1919, 1932), resulted, through their wisdom, in improved diagnosis, treatment, and prevention, and so in an immediate reduction of mortality The second world war again found unacclimatised troops suffering heat casualties in Iraq (Ladell 1944, Lipscomb 1944, Morton 1944, Croom 1944, Shepherd 1945) Between the wars Marsh (1930) gave a scholarly account of the ætiology and prevention of heatstroke among employees of the Anglo-Persian Oil Company, and Whittingham (1930) reported 26 severe cases among Royal Air Force personnel in Iraq

Shipboard Occupation

As table II shows, occupation played a decisive part in the incidence of heat illness on board ship, which is about three times as common in the engine-room, and twice as common in the galley, as it is on deck The 3 patients with heat hyperpyrexia and the 5 with borderline hyperpyrexia were all working in the engine-room Figures in the middle column are derived by an assumption that the average tanker carries deck and engine-room crews and commissariat in proportion 3 2 1

It is obvious that the occupational hazard is caused by the additional heat given out by engines, boilers, and ovens Of 121 patients for whom records of shipboard occupation were obtained, 57% worked in the engine-room Thomson (1946) found engine-room personnel providing 88% of heat illness on H M S *Queen Elizabeth* in the Indian Ocean Crowden (1954) observed the same occupational influence in a Naval ship in the Persian Gulf

Acclimatisation

Though the word "acclimatisation" has enjoyed the dignity of several shades of meaning—e g, the process of settling-down in a new environment, or perhaps the development of equanimity and temperance in face of the hazards and temptations of the Colonies, it is now falling victim to the harsh objectivity of the times and is used synonymously with the phrase "physiological acclimatisation to heat"

Adaptive physiological changes following exposure to unaccustomed heat have been studied extensively in the past twenty years or so (see Bass and Henschel 1956 and *Lancet* 1956) Present-day views may be summarised as follows Exposure to heat causes vasodilation in skin and muscles, without immediate corresponding increase in blood-volume, and this results in cardiovascular instability, with pooling of blood in dilated vessels, and giddiness or syncope on exercise or sudden postural change At this stage, the man is unfit for physical work in the hot environment Adaptive changes include (1) retention of fluid, with an increase in blood-volume which restores cardiovascular stability, (2) a more rapid onset of sweating in response to a rise in body temperature, and (3) an actual increase in the rate of sweating As a result of such changes, exercise in heat does not raise the heart-rate and body temperature so much as it did previously —i e, ability to work in the new environment improves

TABLE II—OCCUPATION OF PATIENTS ON BOARD SHIP

Occupation	All cases	Total at risk	Index
Engine-room	69	36,000	1 500
Deck	33	54,000	1 1600
Commissariat	19	18,000	1 900
Unrecorded	7	—	—

Agreement over the mechanisms of these changes has not yet been reached But the salt retention and reduction in the chloride content of sweat which is seen in people on a low salt intake during the acclimatisation period (Conn 1949, Robinson et al 1950, Weiner and van Heyningen 1952), and the fluid retention which must precede the rise in blood-volume, suggest that the adrenal gland is involved There is already some evidence that urinary excretion of aldosterone rises during acclimatisation (Hellman et al 1956)

Whatever the mechanism, the process is rapid and may be complete within a week There may also be a long-term acclimatisation, developing over months or even years of residence in a hot climate, but to oil-tanker personnel visiting the Persian Gulf only the rapid changes are relevant Sailing from Europe to Kuwait via Suez, they encounter high temperatures particularly after entering the Red Sea After leaving the Suez Canal the modern tanker reaches Kuwait in ten or eleven days By the time they arrived at Mina-al-Ahmadi, our patients had been ill on average for three to five days—i e, their health had broken down within the usual acclimatisation period

Although a few of the 128 were seasoned veterans of the Persian Gulf, 38 (30%) were making their first *summer* trip to it As oil-tankers never tarry, either at loading or discharging ports, their crews continually pass from cool to hot climates and back This may have a bearing on their state of acclimatisation, for Bean and Eichna (1943) found that in young fit men the acclimatisation conferred by one to three weeks' exposure to heat was retained fully for only two weeks Tankers plying directly between Britain and Kuwait spend three continuous weeks in the heat but are then a further three weeks in a cool environment before being once more outward bound from Suez Therefore on each trip to Kuwait their crew may be regarded as unacclimatised, or at least not fully acclimatised, to environmental temperatures east of Suez

Diet, Fluids, and Salt

Critchley (1947) noted that sailors of H M Fleet preferred hot roast joints, potatoes, and suet puddings even in the Persian Gulf in summer-time So do sailors in British oil-tankers today, and their preference cannot be unreservedly condemned Ingestion of large carbohydrate or fatty meals increases the endogenous heat load, and if the meals are followed by work or exercise in high ambient temperatures, this increase may tip the scales in favour of heatstroke. But diet by direction rather than choice can hardly be recommended for sailors already exposed to monotony.

Nowadays, the average tanker has water-cooling devices which supply chilled and palatable water in adequate quantities, and severe water-deficiency is not seen in the crews. Beer is not regularly available to British tanker crews while at sea, but Italian and French sailors are not denied their customary table wine. Heat illness occurred in a relatively high proportion of Italian ships, and of the 6 cases of borderline heat hyperpyrexia 3 were Italian. The association of heat hyperpyrexia with drinking too much alcohol is well known, but it is by no means invariable, and both our patients with heatstroke were British youths who had taken no alcohol at all before their collapse.

Body salt is derived from what is present in food or added to it. A diet containing meat offers approximately 10–15 g. of sodium chloride daily and in cool climates this is greatly in excess of human requirements. The salt habit has been criticised by Ladell (1957) as a luxury and addiction, and Dahl (1958) has suggested that long-confirmed dietary excess of salt may cause "essential" hypertension. Various ethnic groups have been cited as taking no harm from diets yielding less than 5 g. daily—e.g., Lapps, Eskimos, Indonesian peasants, South African bushmen, and North American Indians. Conn and Johnson (1944) showed that *fully acclimatised* Americans could perform hard work in a hot environment yet remain in salt balance on a total salt intake of 5 g. per day.

The sweat of unacclimatised man contains 2–5 g. of sodium chloride per litre. Conn (1949) puts the average as about 4 g. per litre. Hypothetical application of the predicted four-hour sweat rate (P4SR) scale of McArdle el al. (1947) for young, fit, acclimatised men undertaking moderate work in overalls, to dry-bulb and wet-bulb temperatures and air-speeds recorded by one of us (C. S. L.) in the engine-room of a tanker in the Red Sea and Persian Gulf in May, 1956, suggests a loss of up to 6 litres, or more, during a four-hour watch. As the engineers under observation could not have been fully acclimatised, and the actual sweat rates were therefore probably lower than calculated, salt losses may be put at 12–16 g., or more, in the four hours. The experiments of Conn and of others show that in acclimatised men on a low intake of salt the salt content of the sweat may drop to less than 0.5 g. per litre, thereby "saving the day," but the high incidence of salt deficiency (46%) among our 128 patients suggests that dietary salt intake was inadequate for the circumstances and that in some individuals reduction of the salt content of the sweat had not developed in time to avert onset of the deficiency state.

Sex and Age

Among 302 cases of heat illness among civilians during heat-waves in Chicago, Cincinnati, and St. Louis, males outnumbered females by 238 to 64 (Gauss and Meyer 1917, Ferris et al. 1938, Austin and Berry 1956). But the sex incidence is of no significance to Persian Gulf shipping, for only a few of the gentler sex sail in tankers—as laundresses or stewardesses. At Mina-al-Ahmadi 4 complained of giddiness, headache, and fatigue, but none were febrile or salt-deficient.

The 128 patients ranged in age from 15–65 years but 70% were between 18 and 40. This merely reflects the age pattern of the sailors at risk. Service personnel and other young men working hard in a hot environment suffer heat illness despite their youth: thus of 733 cases reported from such communities, 90% were below 40 years of age (Wallace 1943, Caplan 1943, Borden et al. 1945, Malamud et al. 1946), whereas when the wide age-range civilian populations of Chicago, Cincinnati, and St. Louis (vide supra) were exposed to heat stress 80% of casualties were above the age of 40. The inference seems to be that increasing age, with the onset of degenerative diseases such as arteriosclerosis, coupled possibly with an increase of the body-mass/surface-area ratio (which to some extent influences efficiency of heat loss), increases susceptibility to heat illness.

Nationality

The racial distribution of the patients—again corresponding to that of the sailors at risk—was British 35, Italian 19, Norwegian 16, German 14, Greek 14, French 11, Dutch 7, Indian 5, Chinese 3, Swedish 2, Spanish 1, and American 1.

Over the survey periods, the national flags which contributed the greater bulk of the shipping were British (391 tankers), Norway (363), Liberia (348), France (124), Panama (115), and Italy (100). Since tankers flying the so-called flags of convenience (e.g., Liberia, Panama) carried mixed crews including Italians and Greeks, an index for nationality incidence is not calculable from these figures. However, the proportion of ships of each flag which provided cases of heat illness may cast some light on the influence of shipboard factors: Italian 9%, Panamanian 8%, Liberian 7.5%, British 7%, Norwegian 6%, and French 4%.

The fact that unacclimatised Caucasians fall victims to heat illness more often than people who live in hot climates has somewhat clouded Western medical teaching on the subject. For example, a current British textbook of medicine says that prickly heat is peculiar to white races, whereas in fact Indians and Arabs are by no means exempt. The truth is that, whereas acclimatisation is important, nationality, per se, is not.

General Health

Syphilis, virus pneumonia, enteritis, appendicitis, and malaria complicated 7 of the 128 cases. In a hot environment, infection and gastrointestinal upsets carry an extra risk because fever, anorexia (with reduced water and salt intake), or vomiting and diarrhœa (with increased loss of water and salt) predispose to heat illness.

Prevention

Pickering (1958) quotes Bertrand Russell to the effect that whereas in older civilisations man adapted himself to his environment, the modern American adapts the environment to suit himself. In the desert hinterland of Kuwait, nomadic Bedouins wear long robes to protect themselves from the fierce heat, and during the hottest part of the day they rest in meditative immobility in the shade of their tents. Beside them, the Western oil-company staff wear light clothes, and display health and vigour in contempt of the same heat—but are able to return periodically to bungalows which are supplied with fans, air-conditioning systems, and refrigerators.

In tankers in the Persian Gulf, prevention of heat illness depends on a compromise between these two concepts. In many such ships, sickbays and messing saloons have been provided with individual air-cooling units, and some of the newer tankers have cabin air-conditioning. Ideally, temperatures in resting quarters should be within the range of human *comfort*, and in working spaces within the levels of human *tolerance* to heat In the summer heat of Kuwait, Europeans feel comfortable and sleep well in rooms cooled to about 78°F (25°C) dry-bulb temperature, and this agrees with figures published for Europeans in similar climates, but it is harder to be dogmatic about upper tolerable limits of environmental warmth for men who are working—except in terms impracticably low for ships' engine-rooms in tropical waters

Information on heat tolerance has been reviewed by Bedford and Tredre (1955), and in relation to prevention of heat incapacitation by Ellis (1955) Several physiological indices of heat stress have been evolved but are too complex to be useful to officers of the mercantile marine

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In summary, heat casualties among young working men who may not be fully acclimatised can be predicted at wet-bulb readings above 90°F (32°C) at sustained dry-bulb readings above about 110°F (43°C) and at above 86°F on the effective temperature scale But there seems to be little advantage in recommending that working spaces in ships in tropical waters be kept below these temperatures if in practice this is unlikely to be possible During the late war it was recommended that in British warships in the tropics the effective temperature should not exceed 86°F, but in August, 1951, effective temperatures in the engine-room of one such vessel in the Persian Gulf were between 90 and 95°F (Crowden 1954), and in May, 1956, in the engine-room of a tanker in the Red Sea and Persian Gulf they varied between 85 and 93°F —with no scarcity of old hands to aver that this was mere child's play and that the " real " heat would begin in July

In such circumstances, heat illness can be prevented only if tanker personnel make concessions to the environment, and if they are to do this they must be told what is necessary, and why it is necessary Minard et al (1957) have shown how the incidence of heat casualties among Service recruits was reduced by limiting certain activities during periods of excessive heat

Captains, chief engineers, and other responsible officers should be aware, for example, of the vague premonitory symptoms of heat distress, and should know that if the environmental heat is barely tolerable to a man standing a four-hour watch, such a man is certainly incapable of performing hard work in the same environment for th period *Completely unacclimatised* apprentices, assistan engineers, and other " first-trippers " should not be allowed to judge their own capabilities, for some are too brave Both the *heatstroke* patients reported here w making their fist trip to the Persian Gulf, and one, w was fortunate to survive, developed hyperpyrexia a coma after working for about an hour on electr repairs in a space above the boilers where the tempe ture (recorded *after* the event) was D B 180°F (82 C)

Considerably more attention to salt intake is a required This is reiteration of advice which has of been given without the desired effect, for Thomson (19 found primary salt-deficiency accounting for 89% heat-illness cases on a troopship, Marriott (1950) regard salt-deficiency in tropical countries as " *perhaps the co* monest of all deficiency states ", and Crowden (19 advised an intake of about 30 g of salt daily for engi room personnel at sea in the Persian Gulf in summ months This figure seems to us rational, and implies t addition, at table, to daily food of three unheaped te spoonfuls of salt (or eighteen enteric-coated salt table each containing 0 65 g)

Finally, in the Red Sea and Persian Gulf people suff ing from anorexia and nausea should not be encourag to cease intake of food, water, and salt, as seems to usual And drugs carried by ships in these waters f treatment of gastrointestinal upsets should not conta atropine, which inhibits sweating

Summary

A vast international fleet of oil-tankers now sails in t Persian Gulf, and heat illness aboard the ships is a serio problem, 128 such cases seen at one port *in the summ* of 1956 and 1957 are reported, among which were 3 cas of heat hyperpyrexia (1 fatal), 5 of borderline he hyperpyrexia, 59 of salt-deficiency heat exhaustion, 1 anhidrotic heat exhaustion, and 60 of minor heat syn dromes (unclassified) A large proportion of these cas occurred in the month of August each year

Tanker crews going to the Persian Gulf are exposed t heat especially in the ten days after they *leave* the Sue Canal During this period they have to become rapidl acclimatised, or regain the acclimatisation lost *after the* previous voyage The additional heat-stress of engine rooms and galleys accounted for over half the cases

If heat illness is to be prevented aboard *such* vessels responsible officers must have fuller understanding of th risks Crews must be induced to take supplementar salt in quantities sufficient to replace what they lose i sweat, and officers must be readier to limit activity befor it becomes dangerous For saving lives and *safeguardin* health these personal preventive measures are almost a necessary as maximum air-conditioning of the ships

We wish to express gratitude to our many colleagues in Kuwait to Dr Eric Parry, F R C S , chief of Kuwait State Medical Service, fo permission to investigate patients of the *State* clinic on Mina a Ahmadi pier, and to Mr C A P Southwell, C B E , M C , managin director of the Kuwait Oil Company

REFERENCES

Allen, S D , O Brien, J (1944) *Med J Aust* ii 335
Austin M G Berry, J W (1956) *J Amer med Ass* 161 1525
Bass, D E , Henschel, A (1956) *Physiol Rev* 36 128
Bean, M B , Eichna L W (1943) *Fed Proc* 2 144
Bedford T (1946) *Medical Research Council (War) memo* no 17
— Tredre B E (1955–56) *Trans Instn Min Engrs Lond* 115, 210
Blagden, C (1775) *Phil Trans* 65 484
Borden, D L , Wadill, J F , Grier, G S (1945) *J Amer med Ass* 128 1200

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It is not very uncommon, Buchanan and Leavell (1956) traced 186 published cases and added 13 of their own While investigating their own patients with contemporary techniques they found that the prothrombin-consumption test was abnormal in 5 of 6 tested Later, Singer and Ramot (1956) applied the thromboplastin-generation test to the blood of a patient with pseudohæmophilia and showed that there was a deficiency of antihæmophilic globulin, thus confirming the report of Alexander and Goldstein (1953) Reports of antihæmophilic globulin deficiency in von Willebrand's syndrome have since been published by Matter et al (1956), Nilsson et al (1957), and Fessey and Meynell (1957) among others Biggs and Macfarlane (1958) estimated the antihæmophilic globulin deficiency in 15 members of eleven families with the disease, and in 11 of them the antihæmophilic globulin level was reduced to levels between 1 6% and 45%

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Since the three cases have not previously been published, brief clinical notes are given here

Case 1 —A girl, aged 7 years, was referred for investigation with a history of excessive hæmorrhage after trauma No other members of the family were known to be affected, and blood from her parents and a brother, aged 14, was normal At the age of $2\frac{1}{2}$ years she " cut her tonsil on a sweet ", there was profuse bleeding, her hæmoglobin fell to 20%, and she had to be transfused Since then she had had to be transfused on eleven occasions for bleeding after tooth extractions or epistaxes following trauma or infection Large bruises appeared after quite small bumps, but none of the hæmorrhages seems to have been spontaneous The results of blood tests (tables I

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Patient—after being mixed with 10%			
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* Equal volumes of diluted 1 5 Al(OH)$_3$-treated plasma platelet suspension, normal diluted 1 10 serum imidazole buffer pH 7 3 and 0 025 M CaCl$_2$ were mixed together at 37 C for 6 minutes

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DR LEITHEAD AND OTHERS REFERENCES (*continued*)

Caplan A (1943) *Trans Instn Min Metall , Lond* 53, 95
Conn, J W (1949) *Advanc int Med* , 3, 373
— Johnston H W (1944) *J clin Invest* 23, 933
Critchley, M (1947) *Brit J industr Med* 4 164
Croom, J H (1944) *J R Army med Cps*, 83, 288
Crowden, A J P (1954) Medical Research Council Rep , R N P 54/806
Dahl, L K (1958) *Nature, Lond* 181, 989
Dreosti, A O (1937) *S Afr J med Sci* 2, 29
Eichna, L W , Ashe, W F , Bean, W B , Shelley, W B (1945) *J industr Hyg* 27 59
Ellis, F P (1955) *Milit Med* , 116, 323
Fantus, B (1936) *J Amer med Ass* 107, 14
Ferris, E B Blankenhorn, M A , Robinson, H W , Cullen, G E (1938) *J clin Invest* 17, 249
Friend, N B (1932) *Med J Aust* i 232
Gauss, H , Meyer, K A (1917) *Amer J med Sci* 154, 554
Haldane J S (1905) *J Hyg , Camb* 5 494
Harris, T A B , Hutton A M (1956) *Lancet*, ii, 1024
Hearne, K G (1919) *Brit med J* i, 516
— (1932) *Med J Aust* i 226
Hellmann, K., Collins K J , Gray, C H , Jones, R M., Lunnon, J B , Weiner, J S (1956) *J Endocrin* 14 209
Horne, G O , Mole R H (1950) *Trans R Soc trop Med Hyg* 44, 193
Jelliffe, D B (1958) *ibid* 52, 71
King E J (1951) Micro Analysis in Medical Biochemistry
Ladell, W S S (1957) *Trans R Soc trop Med Hyg* 51, 189
— Waterlow J C , Hudson M F (1944) *Lancet*, ii, 491, 527
Lancet (1956) i, 270
Leithead C S , Wilkinson, W M (1958) *Trans R Soc trop Med Hyg* 52, 19
— Leithead, L A , Lee, F D (1958) *Ann trop Med Parasit* (in the press)
Lindsay, P (1936) *Kings of Merry England* (Quoted by Macpherson 1949)
Lipscomb, F M (1944) Medical Memorandum no 5 D D M S , War Office, London
Maclean, K S (1943) *J R Nav med Serv* 29 31
Macpherson R K (1949) Tropical Fatigue Brisbane
Malamud, N Haymaker W , Custer R P (1946) *Milit Surg* 99 397
Marriott H L (1950) American Lecture Series no 32 Springfield, Ill
Marsh, F (1930) *Trans R Soc trop Med Hyg* 24, 257
McArdle, B , Dunham, W Holling H E , Ladell, W S S , Scott J W , Thomson, M L Weiner, J S (1947) Medical Research Council Report, R N P 47/391
Minard D , Belding, H S , Kingston, J R (1957) *J Amer med Ass* 165 1813
Morton, T C (1944) *Trans R Soc trop Med Hyg* 37 347
O Brien, J P (1948) *Arch intern Med* 81, 799
Pickering, G (1958) *Lancet* i, 59
Robinson S , Kincaid R K Rhamy, R K (1950) *J appl Physiol* 3 55
Sargent F ii, Slutsky M S (1957) *New Engl J Med* 256 401, 451
Schickele, E (1947) *Milit Surg* 100 235
Shattuck, G C Hilferty M F (1936) *New Engl J Med* 214, 458
Shepherd H M D (1945) *J R Army med Cps* 84 1
Smith F E (1957) Medical Research Council Report, R N P 57/883
Stenning, J C (1945) *J R Nav med Serv* 31, 129 195
Stoddart, J C (1958) *Brit med J* i 443
Thomson M L (1946) Medical Research Council Report, R N P 46/345
Wallace A W (1943) *Milit Surg* 93, 140
Whittingham H E (1930) *Trans R Soc trop Med Hyg* 24 285
Willcox W H (1920) *Brit med J* i 392
Wolkin J , Goodman J I , Kelly W E (1944) *J Amer med Ass* 124 478
Weiner J S (1938) *J industr Hyg* 20 389
— Hevningen R E van (1952) *Brit J industr Med* 9, 56
— Horne G O (1958) *Brit med J* (in the press)
— Lind A R (1955) *Manager*, 23, 853

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Gauss, H , Meyer K. A. (1917) *Amer J med Sci* 154, 554
Haldane J S (1905) *J Hyg , Camb* 5, 494
Harris, T A. B , Hutton, A. M (1956) *Lancet*, ii, 1024
Hearne, K G (1919) *Brit med J* i, 516
— (1932) *Med J Aust* i, 226
Hellmann, K., Collins K J., Gray, C H , Jones, R. M., Lunnon, J B , Weiner J S (1956) *J Endocrin* 14 209
Horne, G O , Mole R. H (1950) *Trans R Soc trop Med Hyg* 44, 193
Jelliffe, D B (1958) *ibid* 52, 71
King E J (1951) Micro-Analysis in Medical Biochemistry
Ladell, W S S (1957) *Trans R Soc trop Med Hyg* 51, 189
— Waterlow J C , Hudson, M F (1944) *Lancet*, ii, 491, 527
Lancet (1956) i 270
Leithead C. S , Wilkinson W M (1958) *Trans R Soc trop Med Hyg* 52, 19
— Leithead, L A , Lee, F D (1958) *Ann trop Med Parasit* (in the press)
Lindsay, P (1936) *Kings of Merry England* (Quoted by Macpherson 1949)
Lipscomb, F M (1944) Medical Memorandum no 5 D D M S , War Office London
Maclean, K. S (1943) *J R Nav med Serv* 29 31
Macpherson R K. (1949) Tropical Fatigue Brisbane
Malamud, N Haymaker, W Custer R P (1946) *Milit Surg* 99 397
Marriott H L. (1950) American Lecture Series no 32 Springfield Ill
Marsh, F (1930) *Trans R Soc trop Med Hyg* 24 257
McArdle, B , Dunham, W , Holling, H E , Ladell W S S , Scott J W Thomson M L , Weiner, J S (1947) Medical Research Council Report, R N P 47/391
Minard D Belding, H S , Kingston J R. (1957) *J Amer med Ass* 165, 1813
Morton T C (1944) *Trans R Soc. trop Med Hyg* 37, 347
O Brien, J P (1948) *Arch intern Med* 81, 799
Pickering G (1958) *Lancet* i, 59
Robinson S Kincaid R K. Rhamy, R. K. (1950) *J appl Physiol* 3, 55
Sargent F ii Slutsky M S (1957) *New Engl J Med* 256, 401, 451
Schickele, E. (1947) *Milit Surg* 100, 235
Shattuck G C Hilferty M F (1936) *New Engl J Med* 214 458
Shepherd H M D (1945) *J R Army med Cps* 84 1
Smith F E. (1957) Medical Research Council Report R.N P 57/883
Stenning J C (1945) *J R Nav med Serv* 31, 129, 195
Stoddart, J C (1958) *Brit med J* i 443
Thomson M L. (1946) Medical Research Council Report R N P 46/345
Wallace A W (1943) *Milit Surg* 93 140
Whittingham, H E (1930) *Trans R Soc trop Med Hyg* 24, 285
Willcox W H (1920) *Brit med J* i 392.
Wolkin J , Goodman J I , Kelly, W E (1944) *J Amer med Ass* 124, 478
Weiner J S (1938) *J industr Hyg* 20 389
— Heyningen, R. E. van. (1952) *Brit J industr Med* 9, 56
— Horne G O (1958) *Brit med J* (in the press)
— Lind, A R (1955) *Manager*, 23, 853

and II) show the typical combination of prolonged bleeding-time and normal clotting-time with normal platelet-count, the thromboplastin-generation test gave results showing a deficiency of antihæmophilic globulin The patient was admitted to hospital for removal of two teeth, and three transfusions in nine days were needed to control the bleeding She has had three further admissions for control of bleeding from her nose, her tonsillar bed, and her gums

Case 2—A boy, aged 8 years, had had frequent epistaxes for five years, sufficiently severe to need blood-transfusion on one occasion He bruised excessively after minor trauma His joints were not affected His father bled unduly after tooth extractions, other members of the family were unaffected, his mother's blood was normal The results of laboratory tests with this patient's blood (tables I and II) show the same combination as in case 1, but the deficiency of antihæmophilic globulin was less severe

Case 3—This boy, aged 11 years, was referred from the Dental Hospital with a history of excessive bleeding after tooth extractions At the age of 5 years removal of a milk tooth had caused severe hæmorrhage, and a blood-transfusion had to be given When he was 7 years old he had two weeks in hospital after tooth extraction, but the bleeding was controlled without transfusion He also bruised excessively after minor trauma No other members of the family were significantly affected, and no clotting anomaly was found in his mother's blood Laboratory tests with his blood gave results very similar to those of the two other patients

Methods

Blood-clotting tests—These were made essentially as described by Biggs and Macfarlane (1957), imidazole buffer pH 7 3 was added to the incubation mixture in the thromboplastin-generation test

Bridge anticoagulant—To determine whether or not this blood-clotting inhibitor was present in the plasma, the method described by Nour-Eldin and Wilkinson (1958a) was used In this method undiluted aluminium-hydroxide-treated plasma is used in the incubation mixture, and the activity of plasma thromboplastin formed is tested on normal as well as patient's citrate-plasma substrate

Results

Table I shows that the three patients had blood-clotting times, one-stage prothrombin-times, prothrombin-consumption indices, and clot retractions within the normal ranges, but they had prolonged bleeding-times Hess test (capillary fragility) at a pressure of 80 mm Hg for five minutes gave positive results in all instances The nail-bed capillaries, however, showed no abnormality when seen magnified 20 times by Zeiss binocular Paper electrophoresis, using barbitone buffer pH 8 6, showed normal bands for the serum-proteins

The results of the thromboplastin-generation tests are shown in table II Antihæmophilic globulin was deficient in the plasma of all the patients, but the serum factors were normal The patients' platelets were fully active when used in this test Table II also shows the effect of mixing each patient's plasma with plasma from another source, the generation of plasma-thromboplastin is much improved on adding plasma from sources other than hæmophilic patients Furthermore, the addition of antihæmophilic globulin separated from pig's plasma (Bidwell 1955) corrected the defect

The results of testing for Bridge anticoagulant are shown in table III In this test the technique of the clotting-thromboplastin-generation test is used, and the clotting-times of the citrate-plasma substrate, using either normal plasma or the patient's plasma, are compared In hæmophilia the clotting-time with patient's-plasma substrate is longer than with normal substrate, and the difference is greater on using undiluted $Al(OH)_3$-treated plasma in the incubation mixture (Nour-Eldin and Wilkinson 1957, 1958a) Table III shows that no such differences were found in any of the three patients, therefore Bridge anticoagulant was absent

TABLE III—TEST FOR BRIDGE ANTICOAGULANT

Case	$Al(OH)_3$-plasma in incubation mixture	Substrate clotting-time (sec)†	
		Normal plasma substrate	Patient's plasma substrate
1	Diluted 1 5	34	34½
	Undiluted*	34½	35
2	Diluted 1 5	15½	17
	Undiluted*	14	14
3	Diluted 1 5	24	24½
	Undiluted*	20	20

* Undiluted $Al(OH)_3$-treated plasma was used in the incubation mixture, 0 05M instead of 0 025M $CaCl_2$ was added, otherwise reagents were the same as in table II

† Same procedure as in table II

Discussion

When a deficiency of antihæmophilic globulin was found in the blood of patients with von Willebrand's syndrome, the link with hæmophilia was apparently strengthened, but our demonstration of the absence of Bridge anticoagulant distinguishes it from both classical hæmophilia and Christmas disease, and fits in with the different type of inheritance and the really different clinical picture In view of this distinction we think that the name "vascular hæmophilia" should not be used "Pseudohæmophilia" seems to be more suitable because it at least indicates that there are resemblances to hæmophilia, notably as regards the deficiency of antihæmophilic globulin Unfortunately pseudohæmophilia is rather a vague title, having been used as a synonym for many blood-clotting defects and vascular abnormalities which bear some clinical resemblance to classical hæmophilia but differ from it in certain laboratory or genetic aspects Another reason for avoiding the use of this title is apparent from the present work, unlike classical hæmophilia, the plasma of these patients is devoid of Bridge anticoagulant Accordingly we prefer to report these cases as "antihæmophilic-globulin deficiency associated with capillary defect" So long as this deficiency is present, it is clear that, for treatment of continued bleeding, fresh blood—i e, blood within two hours of being drawn from the donor—or antihæmophilic factor concentrate should be used, in the absence of the antagonistic Bridge anticoagulant the therapeutic effect should be good

The finding that the platelets were normal in number, morphology, clot retraction, and activity in the generation of plasma-thromboplastin indicates that faulty capillaries are most probably the cause of prolonged bleeding-time With the methods available at present we could not detect the true nature of the defect producing this anomaly in our patients It may be due to a histological abnormality

It is remarkable that no hæmarthrosis or spontaneous visceral bleeding developed in the three patients reported here, in spite of their having a prolonged bleeding-time and increased capillary fragility, thus confirming the observation of Nour-Eldin and Wilkinson (1958b) that these manifestations are related to the concentration of Bridge anticoagulant rather than the level of antihæmophilic globulin

Summary

Three cases of von Willebrand's syndrome, so-called pseudohæmophilia, are briefly described, a deficiency of antihæmophilic globulin was found in their plasma

The Bridge anticoagulant, present in true hæmophilia and in Christmas disease, was absent from the blood of these patients

It is suggested that von-Willebrand's syndrome is a distinct entity and is not a variety of classical hæmophilia, it should be considered as a deficiency of antihæmophilic globulin associated with capillary defect

REFERENCES

Alexander, B , Goldstein, R (1953) *J clin Invest* 32, 551
Bidwell, E. (1955) *Brit J Hæmat* 1, 386
Biggs R., Macfarlane, R. G (1957) Human Blood Coagulation and its Disorders Oxford
— — (1958) *Brit J Hæmat* 4, 1
Buchanan, J C., Leavell, B S (1956) *Ann intern Med* 44, 241
Fessey, B M Meynell M J (1957) *Brit med J* ii, 391
Matter, M , Newcomb, T F , Melly, A , Finch, C A. (1956) *Amer J med Sci* 232 421
Nilsson, I M., Blombäck, M A , von Francken, I (1957) *Acta med scand* 159, 35
Nour-Eldin, F , Wilkinson, J F (1957) *Nature, Lond* 180, 990
— — (1958a) *Brit J Hæmat* 4 38
— — (1958b) *ibid* (in the press)
Singer, K., Ramot, B (1956) *Arch intern. Med* 97, 715

KLINEFELTER'S SYNDROME .

GENETIC STUDIES

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IT is now well known that many cases of Klinefelter's syndrome are chromatin-positive by Barr's method of nuclear sexing, and it is generally accepted that the finding of chromatin-positive nuclei indicates the presence of the female pair of XX chromosomes (Lennox 1956), hence these apparently very nearly normal males are " genetic " females with sex reversal

There has been much speculation about the mechanism involved (see especially Plunkett and Barr 1956, Segal and Nelson 1957, Witschi et al. 1957, Danon and Sachs 1957, Grumbach et al 1957) It has often been suggested that the defect is genetic (Reifenstein 1947, Sniffen et al 1951, De la Balze et al 1952, Sohval and Soffer 1953, Grumbach et al 1957) Familial transmission through more than one generation has, however, only once been recorded (Reifenstein 1947) and was thought in that family, in which transmission was maternal, to be due to a sex-linked recessive type of inheritance (Reifenstein 1957, cited by Grumbach et al 1957) Affected sibships have more often been recorded (Nadler et al 1950, Sohval and Soffer 1953, Bunge and Bradbury 1956, Grumbach et al 1957) Associated conditions include oligophrenia (Pasqualini et al 1957, Ferguson-Smith 1958) and dystrophia myotonica (Nadler et al 1950, Grumbach et al 1957, Siebenmann 1957) Sibships have been reported with chromatin-positive and chromatin-negative cases (Bunge and Bradbury 1956, Grumbach et al 1957) and with cases of Klinefelter's syndrome and Turner's syndrome (Bassoe, 1956) There is thus some evidence of the presence of a genetic defect, but little of its nature

Attention has been chiefly concentrated in recent papers on the more striking chromatin-positive (genetic female) cases Our own first studies in this field (Ferguson-Smith et al 1957) had as one of their main results the unequivocal demonstration of a histological difference between the testes of chromatin-positive and chromatin-negative patients* but left us, in spite of this, with a clinical impression that the resemblances between the two varieties of the disease are as important as the differences The studies reported here suggest that the defect is genetic and that the mechanisms operating in chromatin-positive and chromatin-negative cases are similar in type They also provide evidence about the nature of the mechanism

The present study is confined almost entirely to accessible patients from the series (now including less than a third of the chromatin-positive cases identified in this area) of 27 cases, 16 chromatin-negative and 11 chromatin-positive, collected by scrutiny of biopsy specimens and re-study of all available patients with azoöspermia and severe oligospermia who had attended a male subfertility clinic in 1955 and 1956 (Ferguson-Smith et al 1957)

Case 9 (table I) and case 24 (table II) did not belong to our original series Case 9 was noticed when he attended a urology clinic with an unrelated complaint He was married and had previously been investigated for subfertility elsewhere Case 24 was unmarried and was referred from an endocrine clinic for testicular biopsy

The fertility-clinic patients are selected in that they are all married men Compared with other series, ours might

TABLE I—NUMBER OF SIBS AND PARENTS' SIBS OF CHROMATIN-POSITIVE PROPOSITI

Case no	Age (yr)	Sibs		Paternal uncles				Paternal aunts				Maternal uncles				Maternal aunts			
		♂	♀	D	U	C	F	D	U	C	F	D	U	C	F	D	U	C	F
1	29	0	2	9	3	1	4	0	1	0	1	0	1	0	3	1	0	1	2
2	35	0	1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	1	4
3	29	2	2	0	0	0	1	0	0	0	1	0	0	0	2	0	0	0	1
4	36	1	1	0	2	1	2	0	0	0	2	0	1	0	2	0	0	0	2
5	29	1	2	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0
6	35	1	1	0	1	0	1	0	0	1	0	0	1	0	1	0	0	0	3
7	34	0	1	0	0	1	1	0	0	1	0	0	1	0	0	0	2	0	0
8	42	2	3	0	0	0	2	0	0	1	1	0	0	0	1	0	0	0	2
9	39	3	0	1	5	1	0	1	1	0	2	0	1	0	4	0	1	1	3
Total		10	13	10	11	4	12	1	2	4	8	0	5	1	16	1	3	3	17
Proportion of childless to fertile adults (U + C) F					15 12				6 8				6 16				6 17		
Sex ratio (total males total females)		10 13					37 15								22 24				
Average size of family including propositus or parent		3 6							6 8						6 1				

Important families and significant ratios (see text) indicated in bold type
C, married but childless D, died young F, married and fertile U, adult but unmarried

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* Unknown to us, Nelson (1956) had in part anticipated these histological findings

TABLE II—NUMBER OF SIBS AND PARENTS' SIBS OF CHROMATIN-NEGATIVE PROPOSITI

Case no	Age (yr)	Sibs			Paternal uncles				Paternal aunts				Maternal uncles				Maternal aunts			
		♂	♀	?	D	U	C	F	D	U	C	F	D	U	C	F	D	U	C	F
10	32	2	2	5	2	1	0	3	0	0	0	5	0	1	1	0	0	0	0	2
11	29	0	0		0	0	0	3	0	0	1	2	0	0	1	1	0	0	0	1
12	29	0	0		0	1	1	0	0	0	0	2	1	2	1	0	0	0	0	1
13	29	5	2		0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	2
14	31	0	2		0	1	0	3	0	1	0	1	0	0	0	3	0	0	2	1
15	31	1	2		0	0	1	2	1	1	0	0	0	0	0	0	0	0	1	2
16	32	4	4		0	0	0	2	0	0	0	1	0	2	0	0	0	0	0	3
17	40	3	2		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	37	2	0																	
19	31	1	1		0	0	0	1	0	0	3	0	0	1	0	3	0	0	0	3
20	29	0	1	1	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0	1
21	30	2	2		0	1	0	2	0	0	0	0	0	2	0	0	0	0	0	3
22	38	2	1		0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0
23	39	0	3		0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1
24	40	0	0		0	0	0	1	0	0	0	2	0	1	1	2	1	0	0	0
Total		22	22	6	2	4	2	21	1	2	5	14	1	9	4	12	1	1	3	20
Proportion of childless to fertile adults (U+C) : F					6 : 21				7 : 14				13 : 12				4 : 20			
Sex ratio—total males : total females		22 : 22			29 : 22								26 : 25							
Average size of family including propositus or parent		3·9			4·6								4·6							

Important families and significant ratio (see text) indicated in bold type.
C, married but childless. D, died young. F, married and fertile. U, adult but unmarried.

therefore be expected to contain more superficially normal men and fewer with subnormal intelligence or with major congenital defect. For example, one of our chromatin-positive cases (see figure) is a tall, powerfully built, deep-voiced "male" who shaves daily. Gynæcomastia is absent. Facial and body hair, although somewhat scanty, is well within normal limits. Measurements are moderately eunuchoid (height 1·87 m, span 1·92 m, from crown to pubis 0·89 m, from pubis to sole 0·98 m), but the main pointer to abnormality revealed by clinical examination is the presence of small firm testes, each about 20 mm long. The great ease with which cases like this can be overlooked is of considerable importance in connection with our estimate of the absolute frequency of Klinefelter's syndrome, and with our suggestion that its familial incidence must be higher than is generally recognised.

Superficially normal 'male' who is chromatin-positive.

Absolute Frequency

A rough estimate of the minimal incidence of Klinefelter's syndrome (of some importance as regards its genetics) can be derived from our figures. Most of the subfertility clinic's patients come from a relatively narrow age-range, the decade of maximal attendance with us being 28–37 years. In this decade we have 4 chromatin-positive and 4 typical chromatin-negative patients with Glasgow addresses. The 1,000,000 inhabitants of Glasgow include 72,000 of either sex of this age. If we have collected all the cases in Glasgow, the frequencies indicated are 1 : 18,000 of each. But not all such persons marry, not all married patients seek advice for their sterility, and not all persons seeking such advice are referred to this clinic. Clearly, even in this decade we cannot have collected all the cases in Glasgow into this one series. We do not think that any random or unrecognised errors in our estimate can counterbalance these factors, and conclude that the true frequency of both chromatin-positive and chromatin-negative varieties of the syndrome can hardly be less than 1 in every 10,000 (reputed) male births.

Family Studies

None of our patients, so far as we know, are related, and it was impossible to examine more than a fraction of the relatives, but important information was obtained by careful questioning of 25 of our patients. These results show one minor discrepancy from their earlier presentation in preliminary form (Stewart et al. 1957), 1 chromatin-negative case having been eliminated because of doubt over the significance of the biopsy finding. (An exact histological definition of chromatin-negative Klinefelter's syndrome has not yet, we believe, been achieved but a more detailed consideration of our present views on this question is to be published elsewhere [Ferguson-Smith et al. 1958].)

Propositi.—Associated inherited defects were inconspicuous. Some of our patients were clearly of low intelligence, but formal intelligence testing was not done.

Sibs.—One of our chromatin-negative patients (case 18) has a brother, also chromatin-negative, who shaves once a week and is grossly eunuchoid (height 1·70 m, span 1·85 m) but has testes of normal size. His only other brother is married and has three children. Since the family are refugees from Central Europe, details of the parental generation are unavailable. None of our other patients has reported any significant deviation of the sex ratio of the sibs (tables I and II). The average age is too low for accurate estimates of childlessness, but many are married and fertile.

Parents' sibs.—Among the aunts and uncles of the propositi are most curious anomalies. Essentially they consist in an excess of childless uncles, paternal in the chromatin-positive cases (table I) and maternal in the chromatin-negative cases (table II). In the latter group there is no excess of uncles, but in the families with chromatin-positive propositi there are an excess of paternal uncles and a deficiency of paternal aunts, shown by disturbance of the sex ratio.

In calculating the proportion of childless to fertile adults we have omitted those who died young (though we have included them in calculating the sex ratio). We have, however, included the unmarried (of marriageable age) in estimating childlessness. Failure to marry seems to be as distinct a characteristic of these families as infertility when married, and, if some of these childless uncles are examples of Klinefelter's syndrome (or something closely allied to it), eunuchoidism and lack of sexual drive may well have been an important factor. Two figures in table I require brief comment.

(1) The 10 who "died young" include 9 members of a single family with the remarkable sex ratio of 18 males to 2 females. 4 were killed in a single accident, and 5 died in the 1914–18 war, so the natural suspicion that the high death-rate is due to congenital defect of some kind is unjustified.

(2) There is a high ratio (6 : 8) of childless to fertile paternal aunts, but this is based on relatively small numbers and is not formally significant, and we have assumed it to be due to chance.

As regards the individual families, the excess of childless uncles is limited to 3 of 9 chromatin-positive and 5 of 15 chromatin-negative cases. The three affected families with chromatin-positive propositi all show an abnormal sex ratio in the parental generation. No abnormal sex ratio can be shown in the propositi's own generation, nor (though this is less important, because many of the sibs are still young) any excess of infertility. The high average size of family in the parental generation in table I has probably helped to make the effect obvious. However, if all the cases were familial, some abnormality of the sex ratio among sibs would have been expected in spite of the smaller families. We must therefore conclude that only some of the cases are familial, the tabulated figures suggest about a third in both varieties of the syndrome, but a much larger series would be necessary to establish this with any exactitude.

Calculation of Significant Differences

Table I.—The proportion of childless to fertile adults for paternal aunts, maternal uncles, and maternal aunts of chromatin-positive propositi are 6 : 8, 6 : 16, and 6 : 17 respectively, but these three groups belong statistically to the same population, and therefore the proportions can be combined (18 : 41). The proportion for paternal uncles (15 : 12) differs from the combined proportion and the difference is significant ($\chi^2=4{\cdot}914$, $p<0{\cdot}05$). The sex ratio of males to females at birth is 106 : 100, therefore the expected ratio for 52 paternal uncles and aunts is 26·8 : 25·2. The discovered sex ratio (37 : 15) differs from this, and the difference is significant ($\chi^2=8{\cdot}081$, $p<0{\cdot}01$).

Table II.—A similar calculation for relations of chromatin-negative propositi shows a proportion for maternal uncles (13 : 12) different from the combined proportion for the others (17 : 55), and the difference is significant ($\chi^2=6{\cdot}898$, $p<0{\cdot}01$).

Twinning

Our earlier histological work suggested analogies (which still hold in some respects) between the sex-reversed gonad of chromatin-positive Klinefelter's syndrome and the partially sex-reversed ovary of the freemartin in cattle (Lillie 1917). We therefore paid special attention to the incidence of twins in the present families. We know of no chromatin-positive patient with Klinefelter's syndrome who has had a normal male twin, so the direct comparison with the freemartin fails at once. Moreover there are three known cases of human dizygotic twins in which blood-group studies have proved the occurrence of intrauterine circulatory mixing, and each consists of a male and a normal (proved fertile in two cases) female (Dunsford et al. 1953, Booth et al. 1957, Nicholas et al. 1957). However, if our cases came from families with a high incidence of twinning, it might have been worth considering the possibility of death in utero of a male twin which had initiated sex-reversal changes, an unlikely but not wholly indefensible hypothesis. However, our data (table III) show no significant excess of twins among the families of the propositi and lend no support to the hypothesis that these patients may be freemartins.

TABLE III—INCIDENCE OF TWINS IN FAMILIES OF PROPOSITI

—	Families of 9 chromatin-positive patients			Families of 15 chromatin-negative patients		
	Total no. of individuals	Pairs of twins	Families with twins	Total no. of individuals	Pairs of twins	Families with twins
Propositi and siblings	32	1	1	65	1	1
Nephews and nieces	33	0	0	80	2	2
Parents, uncles, and aunts	115	4	2	130	0	0
Total	180	5	3	275	3	3

Colour-blindness

Colour-blindness, the commonest readily demonstrable sex-linked recessive character, can be used to distinguish groups of individuals with one X chromosome, in whom it is common, from those with two, in whom it is rare. Polani et al. (1956) applied this reasoning successfully to Turner's syndrome, and Bishop et al. (1956) suggested that the method might be used in Klinefelter's syndrome. We therefore tested colour-vision in most of our patients. Proof of a negative is needed with the chromatin-positive cases, and this will need a very large series, it is hoped, however, that the collected material of Dr Polani, to which our own cases are being added, will soon reach levels of statistical significance. Colour-blindness has, however, so far been found only in our chromatin-negative cases, and it seems already reasonable to predict that the method will again serve to prove that nuclear sexing has been a reliable index of the number of X chromosomes present (Polani et al. 1957).

Discussion

The present series is unusual in several respects. It was collected in a comparatively short time from a two-year sample of patients attending a male subfertility clinic, a highly specialised field which apparently has not hitherto been systematically explored for this purpose. From this sample, unselected in other ways, we calculated that the incidence of both chromatin-positive and chromatin-negative Klinefelter's syndrome is at least 1 of each in every 10,000 male births. The condition is clearly much more common than had previously been supposed. It follows that many patients with Klinefelter's syndrome go through life undiagnosed, and in fact very few of the present series had been labelled "Klinefelter's syndrome" until after the present investigation had started.

Another very important feature of the present series is the relative normality of outward appearance of many of our patients (see figure). We have previously noted (Ferguson Smith et al. 1957) that several of our patients, including 4 chromatin-positive, had spermatozoa in their seminal fluid when first seen, and it is clear that few of the cases conform to, or could be recognised from, the classical descriptions of the syndrome (Klinefelter et al 1942) or its modifications (Heller and Nelson 1945, Howard et al 1950) Yet the concurrence of testicular histology, hormone assays, and nuclear sexing makes it certain that these cases belong to the same group as the more obvious examples

With greater awareness, diagnosis becomes easier, and the two clinicians among us have already begun to recognise the condition in patients referred for totally unrelated complaints The use of buccal smears for nuclear sexing makes diagnosis of the chromatin-positive cases easy and certain, but equally confident diagnosis of chromatin-negative cases requires biopsy, although the condition can be suspected from the clinical appearances and to some extent confirmed by the pattern of excretion of hormones It will therefore be difficult to establish the true incidence of chromatin-negative cases In contradistinction to most previous studies our own suggests that chromatin-negative cases are at least as common as the chromatin-positive variety

Our crucial finding is the excess of childless uncles (tables I and II) A possible attractive explanation is the presence, in the families concerned, of a substantial number of unrecognised cases of Klinefelter's syndrome The existence of individuals who should have occupied the position of paternal aunts to our chromatin-positive patients but have apparently been sex-reversed into sterile " males " would explain both the high incidence of childlessness and the change in the sex ratio In the families of our chromatin-negative patients a corresponding number of affected males on the maternal side would produce a similar incidence of childlessness, but, since the sex is not reversed, the sex ratio would not be affected

There are two difficulties in accepting this

(1) We have not yet proved that any of our childless uncles have Klinefelter's syndrome, but this we believe to be solely due to accidental circumstances which have made it impossible to examine members of the most important families (Hearsay evidence of small testicles has been obtained in 1 case Efforts are being continued, but many of the males concerned are dead or otherwise inaccessible)

(2) Sibships containing several cases of Klinefelter's syndrome should be common, whereas only a few familial cases have been published This seems to be a serious objection to the theory, but may only mean (as emphasised above) that the great majority of cases go completely unrecognised

The somewhat complex genetic implications can only briefly be considered here We have been very much influenced by a strong clinical impression that chromatin-positive and chromatin-negative cases are variants of the same syndrome We therefore accepted the evidence of tables I and II as suggesting not only a genetic mechanism but also similar modes of inheritance, it also provides evidence of the nature of this mechanism

(1) The presence in two generations—presumptive in our cases and established in Reifenstein's (1947)—suggests a dominant character

(2) The seeming transmission by the parent of sex opposite to the presumptive genetic sex of the patient indicates that the condition is sex-controlled (A sex-controlled condition is one in which expression of a defect is limited to one or other sex)

(3) This dominant character seems not to be sex-linked (carried on the unpaired portion of the X chromosome), because some of the chromatin-positive patients with apparently affected paternal uncles had fertile paternal aunts The defect therefore seems to be autosomal (The colour-blindness data, which strengthen the view that chromatin-positive patients were genetic females (XX), is further evidence that the sex chromosomes are normal)

The defect must arise by gene mutation or by chromosomal aberration Possibly more than one mechanism may operate, but only a chromosomal aberration can readily explain the association with other hereditary conditions and the occurrence of chromatin-positive and chromatin-negative cases in a single sibship The most hopeful line of explanation invokes the balance theory of sex inheritance (Goldschmidt 1955), which recognises the presence, both in males and females, of masculinising (M) factors outside the X chromosomes and probably in a pair of autosomes Danon and Sachs (1957) considered that mutation, a qualitative abnormality involving such an M gene, might be causal in chromatin-positive cases, and a more explicit hypothesis of its mode of action in these cases was put forward in an editorial accompanying their paper (*Lancet* 1957)

We prefer to suppose that the defect is quantitative, with duplication of the M locus in one chromosome of chromatin-positive cases and deletion of this same locus in chromatin-negative cases The chromatin-positive patients would be masculinised females due to effective triplication of the M locus, and the chromatin-negative patients would be feminised males, or at least males of subnormal masculinity, due to deletion of one of the normal two M loci Such a defect must clearly be transmitted by a carrier whose sex was opposite to the (genetic) sex of the propositus, thus explaining the opposed maternal and paternal transmissions of the two varieties of the disorder

We do not wish here to do more than to show, on the evidence of our own cases, that a genetic mechanism appears to be common to both chromatin-positive and chromatin-negative varieties of Klinefelter's syndrome, and that chromosomal aberrations resulting respectively in excess and defect of the number of M genes present afford the best explanation yet available Although translocation (Plunkett and Barr 1956) merits careful consideration, the most probable basis seems to be some form of inversion cross-over

More detailed consideration of the nature of the chromosomal aberration(s) involved must await further data It is clear that further work on the families of patients with Klinefelter's syndrome is required Simple statistics of family size such as we have presented could be readily collected in most cases Special efforts should be directed to finding unsuspected examples of the syndrome in families in which there seems to be a high incidence of childless uncles Families with associated congenital traits also deserve especial attention

We recognise that the evidence we have presented for familial transmission of the syndrome is far from perfect, but we believe we are justified in drawing attention to the possibility, because establishment of a mode of transmission of the defect would greatly clarify our ideas of its fundamental nature

Summary

Klinefelter's syndrome is probably a good deal commoner than is generally realised, an incidence at least 1 10,000 each for chromatin-negative and chromatin-positive varieties being suggested

The possibility of familial transmission, at least in some cases, is indicated by the presence of an excess of childless males among the parents' sibs, limited to the father's sibs (indicating paternal transmission) in the chromatin-positive cases and to the mother's sibs (indicating maternal transmission) in the chromatin-negative cases

In addition to the many members of our own departments who have helped us, we have to thank Dr A D T Govan for hormone estimations, Prof L S Penrose for reading our manuscript, Dr R. A Robb for help with the statistics, and Prof E J Wayne for permission to publish one case

REFERENCES

Bassöe, H H (1956) *J clin Endocrin* 16, 1614
Bishop, P M F, Polani, P E, Lessof, M H (1956) *Lancet*, ii, 843
Booth, P B, Plaut, G, James, J D, Ikin, E W, Moores, P, Sanger, R, Race, R. R. (1957) *Brit med J*, i, 1456
Bunge, R. G, Bradbury, J T (1956) *J Urol* 76, 758
Danon, M, Sachs, L (1957) *Lancet*, ii, 20
De la Balze, F A, Arrillaga, F C, Irazu, J, Mancini, R E (1952) *J clin Endocrin* 12, 1426
Dunsford, I, Bowley, C C, Hutchison, A. M, Thompson, J S, Sanger, R., Race, R R (1953) *Brit med J* ii, 81
Ferguson-Smith, M A (1958) *Lancet*, i, 928
— Lennox, B, Mack, W S, Stewart, J S S (1957) *ibid*, ii, 167
— — — — (1958) Symposium on Sexual Differentiation Endocrine Society Memoir (in the press)
Goldschmidt, R B (1955) Theoretical Genetics Berkeley, Calif
Grumbach, M. M, Blanc, W A, Engle, E T (1957) *J clin Endocrin* 17, 703
Heller, C G, Nelson, W O (1945) *J clin Endocrin* 5, 1
Howard, R. P, Sniffen, R C., Simmons, F A, Albright, F (1950) *ibid* 10, 121
Klinefelter, H F, Jr, Reifenstein, E C, Jr, Albright, F (1942) *J clin Endocrin* 2, 615
Lancet (1957) ii, 31
Lennox, B (1956) *Scot med J* 1, 97
Lillie, F R. (1917) *J exp Zool* 23, 371
Nadler, C S, Steiger, W A, Troncelliti, M, Durant, T M (1950) *J clin Endocrin* 10, 630
Nelson, W O (1956) *Acta endocr, Copenhagen*, 23, 227
Nicholas, J W, Jenkins, W J, Marsh, W L (1957) *Brit med J* i, 1458
Pasqualini, R Q, Vidal G, Bur, G E (1957) *Lancet*, ii, 164
Plunkett, E R, Barr, M L (1956) *ibid* ii, 853
Polani, P E, Bishop, P M F, Ferguson-Smith, M A, Lennox, B, Stewart, J S S (1957) Symposium, see *ibid* ii, 638
— Lessof, M H, Bishop, P M F (1956) *ibid* ii, 118
Reifenstein, E C, Jr (1947) *Proc. Amer Fed clin Res* 3, 86
Segal, S J, Nelson W O (1957) *J clin Endocrin* 17, 676
Siebenmann R. (1957) Symposium, see *Lancet*, ii, 638
Sniffen, R C, Howard, R. P, Simmons, F A (1951) *Arch Path* 51, 293
Sohval, A. R, Soffer, L. J (1953) *Amer J Med* 14, 328
Stewart, J S S, Izatt, M M, Ferguson-Smith, M A. Lennox, B, Mack, W S (1957) Symposium, see *Lancet*, ii, 638
Witschi, E, Nelson, W O, Segal, S J (1957) *J clin. Endocrin* 17, 737

ACUTE PHARYNGITIS ASSOCIATED WITH ADENOVIRUS TYPE-3 INFECTION

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MOST outbreaks of acute respiratory disease attributed to adenovirus infection have been of pharyngitis associated either with conjunctivitis or with tracheobronchitis and occasionally pneumonia Pharyngoconjunctival fever, as the former syndrome has been called, seemed at first to be due only to type-3 virus (Bell et al 1955, Cockburn et al 1956, Sobel et al 1956), but there is now evidence that types 4, 7, and 14, and perhaps other types, may cause a similar illness (Forssell et al 1956, Kendall et al 1957, van der Veen, personal communication) Most outbreaks of pharyngoconjunctival fever have been in summer, and it has been suggested that swimming-baths may be responsible for spreading infection and perhaps for the conjunctivitis The second syndrome mentioned—acute pharyngitis with frequent involvement of the lower respiratory tract but without conjunctivitis—has been found almost entirely among military recruits in the winter months (Berge et al 1955, Hilleman et al 1955, Andrews and McDonald 1957, van der Veen and Kok 1957) and has been associated with several types of adenovirus, including type 3

The outbreak here described took place in a 'boys' residential public school in Berkshire during February and March, 1957, and was apparently due to type-3 adenovirus Though pharyngitis was the main sign, there was little conjunctivitis and no bronchitis or pneumonia A rather similar epidemic, associated with type-7 virus, in a school in the North of England during the autumn of 1955, was described by Tyrrell et al (1956)

The Epidemic

It is difficult to be certain about the date of the first case, because the epidemic was preceded in January by a small outbreak of a febrile illness often accompanied by severe muscle pains This was thought to be Bornholm disease, but no evidence of Coxsackie virus or of adenovirus infection was found at that time in specimens taken from 10 patients and examined in the laboratory A few cases of pertussis during the same period further complicated the picture However, the accompanying figure shows that there was a major epidemic at the end of February and during March

From Feb 25 until the end of the term the illnesses seemed clinically homogeneous and different from what had gone before During this time 134 (34%) of the 395 boys in the school were admitted to the sanatorium or to a dormitory set aside to take the overflow All the boarding-houses suffered to about the same extent, the only systematic feature apparent in the distribution of cases was that they were more among the young than the old A possible explanation of this was that older boys slept in cubicles and not in dormitories Attack-rates by year of birth were as follows 1938, 8%, 1939, 21%, 1940, 37%, 1941, 31%, 1942, 42%, and 1943, 47% Only 5 adults were affected—3 of 35 masters and 2 of 10 nurses or house-matrons

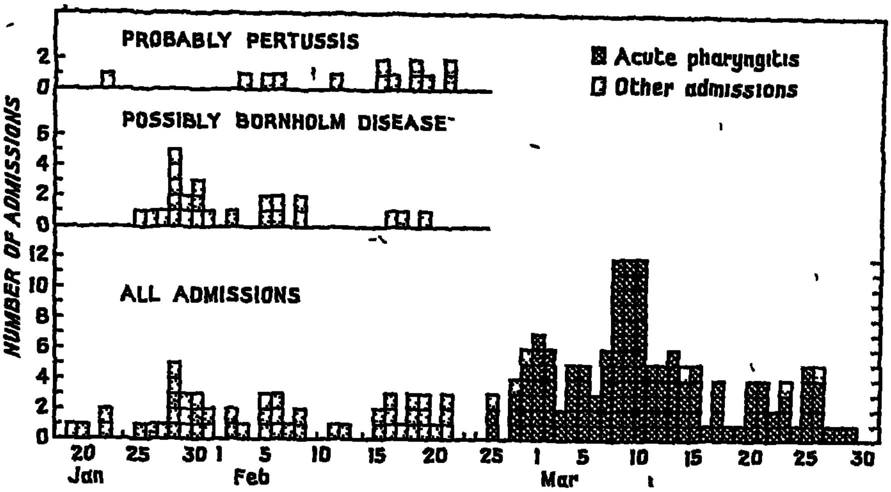
Examination of serial intervals between dates of onset by dormitory gave no indication of the incubation period In 1 boy it must have been at least six days, he left school alone on March 16 to sit an examination in Oxford and became ill on his way back to school on March 22, virus was isolated from a throat swab taken from him on the same day

Clinical Features

The onset of the illness was usually sudden, with pyrexia of 101–103°F falling gradually to normal in four to six days The predominant symptoms were sore throat, headache, and a slight dry cough Nasal symptoms, usually of obstruction, were present in just under half the patients, and sweating was prominent in about a third Other and less common complaints were of hoarseness, pain in or behind the eyes, general muscle pains, and dizziness The fauces were injected, many boys having pin-head vesicles on the soft palate Apart from 2 cases with definite conjunctivitis and 1 with obvious enlargement of the cervical lymph-glands, there was little or no evidence of lymphadenopathy or of conjunctivitis Recovery was usually rapid, the only complications were 2 cases of otitis media, which were treated with penicillin and settled rapidly No symptoms or signs of bronchitis or pneumonia were found Boys who remained febrile for more than four days were treated with penicillin, and this usually coincided with a fall in temperature

Laboratory Methods

Attempts to isolate the virus were made in a similar manner to that described by Kendall et al (1957) HeLa-cell cultures were grown



Daily admissions to school sanatorium

in a medium containing 20% human serum, before inoculation the serum was removed from the cell culture by washing and replaced by a maintenance medium containing 2% rabbit serum 0 2 ml of Hanks' salts solution, into which throat or eye swabs had been broken, were inoculated into each of two tubes of HeLa-cell cultures The cultures were kept for fourteen days and, if negative at the end of this period, were given a blind passage in two more tubes of HeLa-cell culture

When degeneration suspected of being due to an adenovirus occurred, the culture tubes were frozen and thawed, and the fluids were tested by the complement-fixation test for the presence of adenovirus using a known positive serum Viruses found in this way were typed in HeLa-cell cultures containing 0 5 ml of maintenance medium to which was added 0 1 ml of type-specific serum followed by 0 1 ml of suspected virus under test The dose of virus was adjusted to give complete degeneration in two to three days The sera used were those of types 2, 3, 4, and 7, and were supplied by Dr B E Andrews They had been prepared in rabbits which had received a series of intravenous injections of supernatant fluids from HeLa cultures infected with adenovirus prototype strains

The complement-fixation test was performed in the cups of plastic hæmagglutination plates (World Health Organisation 1953) Serum, complement (2¼ M H D), and antigen were mixed in 0 1-ml volumes and incubated at 37°C for one and a half hours, 0 2 ml of a 1% suspension of sensitised sheep red blood-cells was then added After thirty minutes at 37°C the plates were stored overnight at 4°C, and the results were read next morning Titres recorded were the highest serum dilutions showing about 75% or more of the red cells unlysed The antigen was used at the optimal dilution and was prepared from cultures of HeLa cells infected with RI-67 virus (adenovirus type 4) This was supplied by the Standards Laboratory, Colindale

Laboratory Findings

Samples of blood were taken from 11 patients in the acute and convalescent stages Throat swabs for virus-isolation tests were taken from 10 of these and from 4 others 8 of the 11 pairs of sera gave a fourfold or greater rise in adenovirus complement-fixing antibody The 3 negative results were in boys from whom the convalescent-blood specimen was not taken until eight weeks after the onset of illness Complement-fixation tests for influenza A, B, and C, psittacosis, Sendai virus, and *Rickettsia burneti* were all negative and so was the *Streptococcus M G* agglutination test for atypical pneumonia

Adenovirus strains were isolated from 8 of 14 throat swabs tested Serological evidence of adenovirus infection was found in 3 of the failures, the remaining 3 were in boys from whom swabs were not taken till the fifth or sixth day of illness All 8 strains were found to belong to type 3 13 of the 14 throat swabs were tested in fertile hens' eggs for the influenza viruses and found negative

Nose and throat swabs from 42 cases at various stages of the outbreak were examined by Dr N Wood, of the Public Health Laboratory, Reading, who reported a heavy growth of hæmolytic streptococci in 1, a moderate growth in 2, and a scanty growth in 3 1 of the boys with a moderate growth of hæmolytic streptococci developed a scarlatiniform rash, but he also had a fourfold rise in adenovirus complement-fixing antibody

Summary and Conclusion

An epidemic is described of acute pharyngitis in a boys' public school in Berkshire during February and March, 1957

A third of the 395 boys were admitted to the school sanatorium, the attack-rate varying inversely with age

The symptoms and signs were those of acute pharyngitis, only 2 patients had definite conjunctivitis, and none had bronchitis or pneumonia

Laboratory tests on a representative sample of patients indicated that the outbreak was caused by infection with adenovirus type 3

REFERENCES

Andrews, B E, McDonald, J C (1957) *Proc R Soc Med* 50, 753
Bell, J A, Rowe, W P, Engler, J I, Parrott, R H, Huebner, R J (1955) *J Amer med Ass* 157, 1083
Berge, T O, England, B, Mauris, C, Shuey, H E, Lennette, E H (1955) *Amer J Hyg* 62, 283
Cockburn, T A, Rowe, W P, Huebner, R J (1956) *ibid* 63, 250
Forssell, P, Lapinleimu, K, Strandström, H, Oker-Blom, N (1956) *Ann Med exp Biol Fenn* 34, 287
Hilleman, M R, Werner, J H, Adair, C V, Dreisbach, A R (1955) *Amer J Hyg* 61, 163
Kendall, E J C, Riddle, R W, Tuck, H A, Rodan, K S, Andrews, B E, McDonald, J C (1957) *Brit med J* ii, 131
Sobel, G Aronson, B, Aronson, S, Walker, D (1956) *J Dis Child* 92, 596
Tyrrell, D A J, Balducci, D, Zaiman, T E (1956) *Lancet*, ii, 1326
van der Veen, J, Kok, G (1957) *Amer J Hyg* 65, 119
World Health Organisation (1953) *Tech Rep Ser* no 64

TREATMENT OF INGROWING TOENAILS

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ONLY thirty-nine papers wholly on ingrowing toenail seem to have been published in the past fifteen years, three of them in British periodicals (Nuttall 1942, Zadik 1950, Kemp 1955) This comparative silence is not due to universal agreement on the subject, five textbooks of surgery chosen at *random* offer eleven different methods of treatment Usually these methods are not based on explicit pathology, but, when they are so based, usually the statement is made simply that pressure from tight shoes and socks, combined with cutting the nail short, or trimming away its corners, leads to pressure ulceration at the lateral edge of the nail, followed by suppuration and granulation

A fuller account is given (in an article not exclusively concerned with ingrowing toenail) by Lake (1951), who describes two varieties

(1) *Juvenile type*—Commonest in the age-group 14–18, especially in males The nail is flat from side to side, the lateral fold being large and overhanging At first only discomfort is felt Ulceration, suppuration, and granulation follow later Lake doubts if tight shoes are a cause

(2) *Adult type*—Usually after middle age The transverse curvature of the nail is much increased, with the result that the edge digs into the toe It causes discomfort and callosity but seldom suppurates

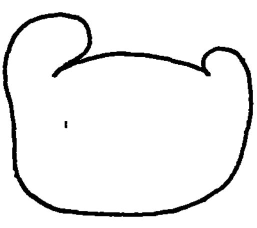


Fig 1—Transverse section of terminal phalanx of hallux with ingrowing toenail of juvenile type

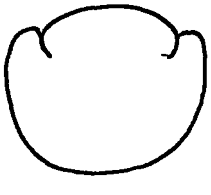


Fig 2—Transverse section of terminal phalanx of hallux with ingrowing toenail of adult type

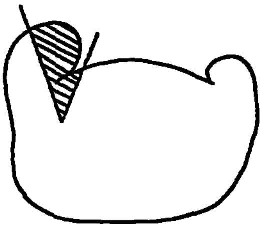


Fig 3—Watson Cheyne's operation shaded area is excised

Pathology

My personal observation confirms Lake's findings Although the age correlation is not invariable, the morphological distinction is real and important, and the terms " juvenile " and " adult " are convenient

In the juvenile type (fig 1) the nail may be normally arched, flat, or even slightly concave The edges are directed outwards, away from the bone Ingrowth may occur at the medial or lateral side or both The toe is often moist, with white macerated skin The affected nail-fold is greatly enlarged, burying the lateral margin of the nail and partly concealing its dorsal aspect. The pulp of the terminal phalanx seems to be abnormally flaccid and yielding, and can be rolled dorsally round the side of the toe, increasing both the width of the phalanx and the depth of the nail-fold To some extent this displacement of the pulp is permanent, but it is momentarily increased with each step as the toe is pressed down From the dorsal aspect the widening of the terminal phalanx is strikingly obvious by comparison with the proximal phalanx (figs 4 and 12) Because of its increased width, the affected phalanx receives an impression on its lateral aspect from the second toe (fig 5), and the sideways and dorsal displacement of the pulp leads to flattening of the plantar surface This throws the weight-bearing point proximally, and a callosity may develop just distal to the interphalangeal skin-crease

Ætiology

Trimming away the corners or lateral borders of the nail is undoubtedly harmful and may precipitate ulceration and sepsis The role of tight shoes is more doubtful. They always offer an easy target for abuse, but it is noteworthy that the affected part is wider than it should be, not narrower, and that females, who are more prone to wear narrow shoes, are less commonly affected than males Lake concurs in disbelieving that shoes are responsible

On the other hand, many of the patients work in gum-boots, or at occupations in which the feet are constantly wet, and some seem to have primary hyperhydrosis The wet macerated skin, which has already been mentioned as a common finding, contributes to the general softening, which allows such ready displacement of the pulp, it also hastens the onset of pressure ulceration at the edge of the nail Laxity of the pulp seems to be the crucial factor,

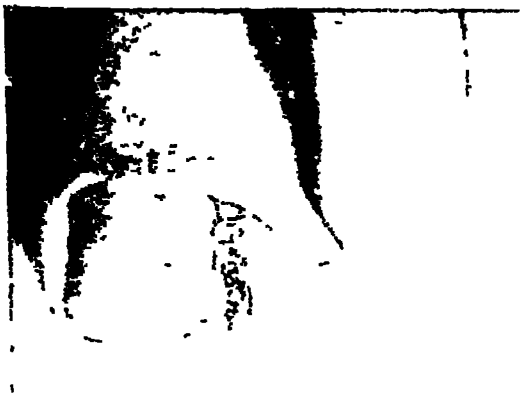


Fig 4—Toe before operation

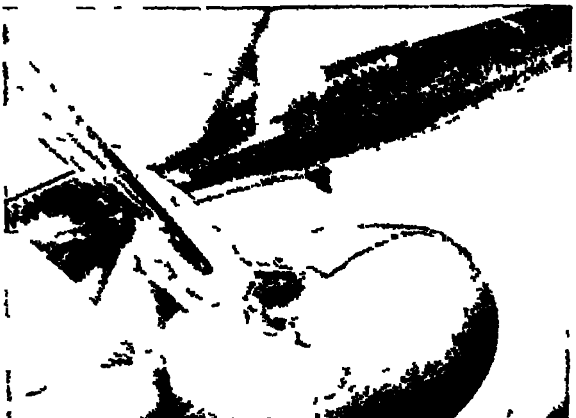


Fig 6—Avulsion of undermined strip

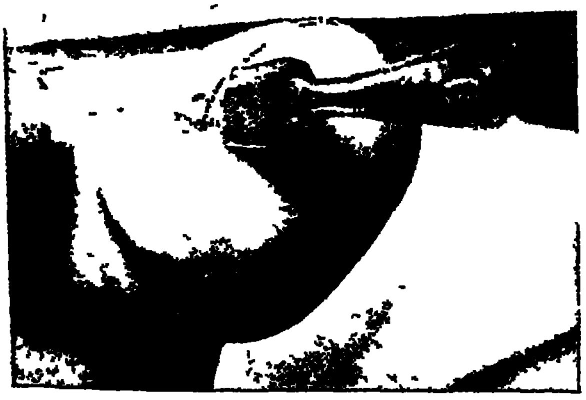


Fig 5—Undermining with blunt dissector

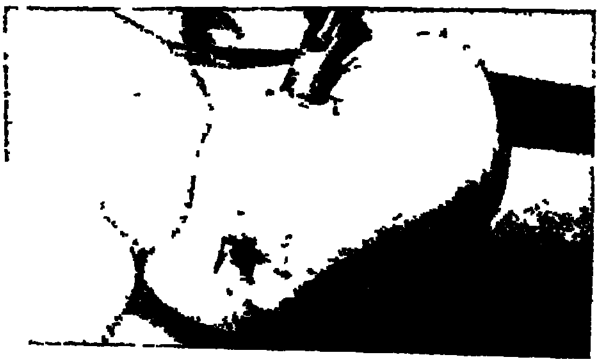


Fig 7—Introduction of scalpel.

however Its cause is not evident, though its effects are clear enough The bony phalanx and nail are firmly bound together as a rigid unit which, when the toe bears weight, the flexors press down into the soft pulp, which streams up round the side of the bone pushing against the edges of the nail and swelling the nail-fold

The adult type (fig 2) is a much less common cause of symptoms The specific feature is a tendency of the edges of the nail to turn in towards the phalanx Softening of the pulp is not found In the absence of diabetes and of arterial occlusion it does not usually cause ulceration

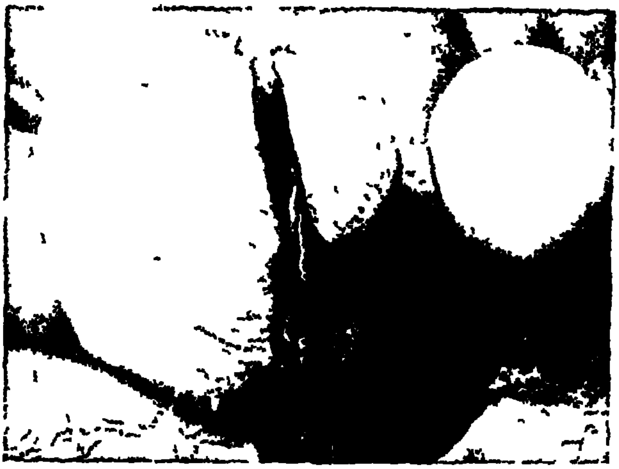


Fig 8—Formation of flap

Treatment

The remedies suggested in standard textbooks include the following

(1) Cutting the nail square, packing cotton-wool beneath the corners, and wearing wide shoes

(2) Thinning the centre of the nail by scraping

(3) Cutting away a V at the centre of the free edge of the nail

(4) Avulsion of the nail with or without curetting away granulations

(5) Filleting the nail-bed off the dorsum of the phalanx

(6) The same, with skin-grafting of the raw area

(7) Zadik's operation (filleting off the proximal portion of the nail-bed, and closure by dorsal skin-flap)

(8) Watson-Cheyne's operation (fig 3)

(9) Willett's operation (see below)

(10) Amputation of half the terminal phalanx, including the nail-bed, and primary closure by plantar flap

(11) Amputation of the terminal phalanx

In the absence of ulceration, suppuration, and granulation conservative measures (1), (2), and (3) usually succeed, especially in lesions of the adult type On the infrequent occasions when infected adult-type lesions (not due to diabetes or to ischæmia) do not yield to conservative methods, amputation of half the phalanx, with ablation of the nail-bed, is satisfactory However, most patients requiring operation have infected juvenile-type lesions

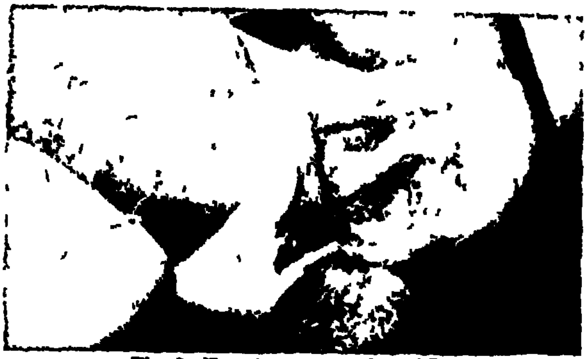


Fig 9—Toe after amputation of flap

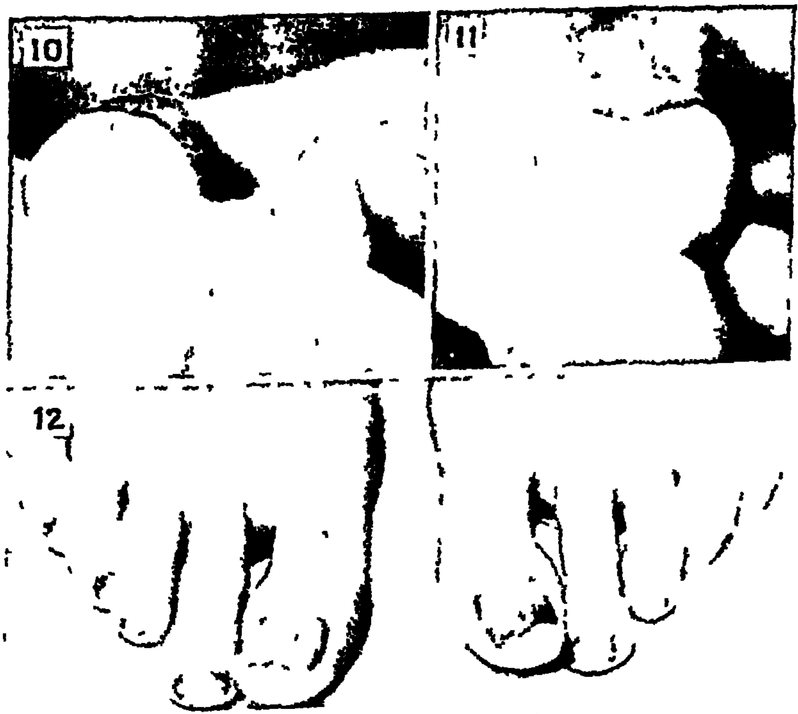
For these the conservative measures (1), (2), and (3) are insufficient Avulsion (4) is followed by recurrence when the nail regenerates, and (5), (6), and (7) are often marred by painful recurrent spicules of nail and produce deformity Watson-Cheyne's operation has both these faults and also leads to recurrences indistinguishable from the original condition The amputations (10) and (11) are mutilating, and occasionally healing is delayed by osteomyelitis or by sinuses

I describe here a new method, similar in principle to Willett's operation, which is suitable for all juvenile-type cases requiring surgery Willett's operation is described as follows (Burrows 1955)

> "This aims at the production of a flat scar along that side of the nail which tends to grow in A tenotome is passed in at the side of the base of the nail, deep to the skin and undercutting it to a width of half an inch The tenotome is then worked forwards to beyond the tip of the nail, thus raising a flap of skin half an inch wide along the whole nail margin, this flap is cut off at its base and the raw area allowed to heal by granulation "

Present Operation (figs 4–9)

The toe is cleansed Digital-nerve block or general anæsthesia is induced A McDonald's blunt dissector is



Figs 10-12—Two years after operation

passed beneath the nail at the affected side, and the strip thus undermined is cut free and avulsed A scalpel is introduced at the proximal end of the groove between nail-fold and nail-bed so as to bisect the angle between the two It is pushed through to emerge from the lateral margin of the toe Its point of emergence should be well down towards the plantar surface, so that the points of entrance and exit are at least half an inch apart. The knife is then advanced distally, cutting a flap consisting of the nail-fold and a substantial strip from the side of the toe (fig 8) The knife is then turned round, the flap is tapered off and amputated at its base, bevelling off the bare area proximally (fig 9) The toe is wrapped tightly in a soft-paraffin gauze bandage, which is left for a fortnight, unless there are signs of gross sepsis The tourniquet shown in the photographs is a great help though not essential

The following points require special emphasis

(1) This operation is unsuitable for the adult type of ingrowing toenail

(2) The knife enters the angle between nail-bed and nail-fold The nail-bed is not cut in any way

(3) It is essential to remove enough soft tissue because the mobile pulp is always ready to roll round the phalanx and create a new nail-fold Any excision less than that illustrated is likely to fail

Results

I have done this operation regularly for the past seven years Properly carried out in appropriate cases, it is always successful It produces no deformity of toe or nail, no discomfort or loss of function, and no recurrence There are no complications such as wound infection, osteomyelitis, and recurrent nail spicules The period of disability is reduced to a minimum because the operation can be done on outpatients on their first visit Suppuration is no contraindication, indeed the operation is a most effective way of terminating sepsis After the bandages have been changed on the fourteenth day, normal walking is possible and the patient can return to sedentary or light work

Figs 10–12 show the result two years after operation The toes are the same ones illustrated in figs 5–9 Although the patient still cuts the corners of the nails rather short, there is now no tendency to ingrowth, because the skin of the new nail-fold is almost level with the nail-bed

REFERENCES

Burrows, H J (1955) *in* Modern Operative Surgery (edited by G G Turner and L C Rogers), p 78 London

Kemp, C E (1955) *Postgrad med J* 31, 558

Lake N C (1951) *Brit med J* i 1072

Nuttall H C W (1941) *Lancet*, ii, 100

Zadik F R (1950) *J Bone Jt Surg* 32B, 66

"With the evolution of man, characterised as it was by delay in development, great prolongation of childhood and resultant consolidation of the family, this pattern of altruistic behaviour must have acquired enormously enhanced importance The size of the unit within which what may now be called ethical conduct prevailed grew larger, from the family to the clan, but between clans the sub-human competition on lines of natural selection persisted The same was true when the welfare unit became the tribe, and eventually the nation, but the relations between nations show only too clearly that there is still a step for man's moral evolution to take in enlarging the welfare unit to encompass the whole of humanity Man's moral evolution is still incomplete"—SIR GAVIN DE BEER, *The Listener*, July 3, 1958, p 12

ULCERATIVE COLITIS

A TEST OF PSYCHOSOMATIC HYPOTHESES

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ULCERATIVE colitis has been claimed to be a member of the psychosomatic group of diseases According to Halliday (1943) a psychosomatic affection is "a bodily disorder whose nature can be appreciated only when emotional disturbances (i e, psychological happenings) are investigated in addition to physical disturbances (i e, somatic happenings)" Apparently some workers regard the case as proven

Sullivan and Chandler (1932) reported a series which they describe as of psychogenic origin, and Sullivan (1940) elaborated these findings with a paper on Psychogenic Factors in Ulcerative Colitis Groen (1947) discussed not only the psychogenesis of the disease but also the use of psychotherapy in its treatment, and this theme has been supported by Daniels (1942), Lindemann (1945), Karush and Daniels (1953) and Craddock (1953) In this country Wittkower (1938) described personality studies in 48 unselected cases and found evidence that "ulcerative colitis is a disease of the mentally ill or maladjusted Almost all the patients showed character disorders, obvious neuroses, or psychoses" With this view Paulley (1956) agrees

Several hypotheses have been advanced to explain the psychosomatic nature of the condition, and these are well reviewed by Engel (1955), who also illustrates (Engel 1954a, 1954b) the inadequacy of those hypotheses which depend on functional diarrhœa being a preliminary feature In his own series (Engel 1954b) of 32 patients 22 presented originally with bleeding, and diarrhœa, when it did occur, was usually secondary On the other hand, support for the "ejection-riddance" theories has come from Grace et al (1951) who, from their studies of 4 patients with fistulæ (2 with ulcerative colitis), conclude that "the colon of man is likely to participate in his reactions to threatening events in his life situation, including those threats which arise out of problems of interpersonal adjustment Changes involving colonic hyperfunctioning at first altogether functional and transitory may when unduly sustained result in structural change and disease"

Though agreeing that personality changes are seen in patients with ulcerative colitis, many do not regard these changes as primary They adopt a "common-sense" view that a person with frequent diarrhœa and bleeding per rectum may well show secondary personality changes, if this were so it would prove a most powerful argument against the psychosomatic theorists Two of the more attractive hypotheses—those of Alexander (1952) and Grace et al (1951)—largely depend on diarrhœa being a reaction to frustration, and, since this symptom has been shown by Engel (1954b) to be the less common presenting feature of the disease, there is good reason for further inquiry into a larger series

Method

A retrospective inquiry into the incidence and order of appearance of each of six main symptoms was undertaken by means of a questionnaire, which was circulated to all 164 members of the Midlands division of the Ileostomy Association 142 replied, and we attribute

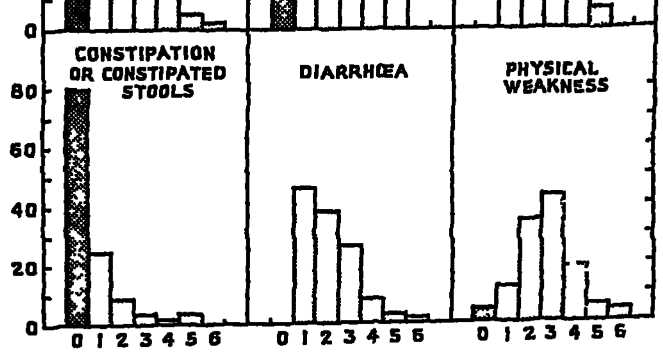
INCIDENCE OF EACH SYMPTOM IN ITS ORDER OF APPEARANCE, LAST COLUMN SHOWS NUMBER OF PATIENTS WHO DID NOT HAVE THE SYMPTOM

Symptoms	Order of appearance						0
	I	II	III	IV	V	VI	
Abdominal pain	23	33	17	16	5	2	25
Anxiety and/or depression	23	16	33	21	13	—	14
Bleeding per rectum	37	48	18	10	6	—	—
Constipation or constipated stools	24	9	3	1	3	—	80
Diarrhœa	47	39	27	7	2	1	—
Physical weakness	5	12	35	43	19	5	4
Total	159	157	133	98	48	8	—

this high return to the fact that the form, though designed by ourselves, had been approved by the secretary of the association and sent out to the members by their officers with an explanatory letter

There are disadvantages in this method, for retrospective surveys are less satisfactory than those planned in advance, and in this particular investigation reliance has to be placed on the memory of patients for symptoms which in about a third of the series had begun five to ten years before We did consider the perusal of case-histories, but soon realised that, no matter how good these may be, a great difference exists between information obtained by various doctors and a standardised series of questions designed to produce answers in numbers We chose the questionnaire, not only because of the greater ease in handling the data derived, but because we wanted to test the method itself The active cooperation of a patient in a therapeutic trial has already been reported by Hogben and Sim (1953), and an Ileostomy Association with a membership of 164 consisting mainly of patients whose diagnosis had been confirmed at laparotomy appeared to us a most suitable medium for this type of investigation

Of the 142 forms returned, 1 was unsigned Confirmation of the diagnosis was sought from the surgeons concerned in all cases and was obtained in all but 3, a further 6 had not had ulcerative colitis Of the 132 who had, 12 returned forms completed in an equivocal manner, and though we had access to most of the information from other sources, we wanted to confine the investigation to data derived from the questionnaire, these were therefore excluded from the study The replies from 120 patients form the basis of this report and are recorded in the accompanying figure



Order of appearance of 6 symptoms in 120 patients with ulcerative colitis

Analysis of Data

Diarrhœa as a presenting symptom is only slightly more common than bleeding (47 37, see table), and therefore the "ejection-riddance" theory finds only very modest support On the other hand, bleeding presents initially more commonly than most psychosomatic theorists would have us believe, perhaps therefore an alternative hypothesis is needed Engel (1955) has elaborated one, but, since it depends on the fact that bleeding is the prime feature in the majority of cases, it cannot be considered adequate for the majority of the present series He does, however, stress that with a careful personal analysis of data (Engel 1954b) more patients admit to bleeding as a first symptom than to diarrhœa, and it may be that the questionnaire did not supply this information accurately This is a valid argument, but the value of the present method cannot be adequately tested by argument, but only by a carefully controlled prospective inquiry, which we propose to do

Anxiety and depression are traditionally regarded as important precipitating factors in the illness, yet they provide the first symptoms in only 23, these conditions are so common in the general population that this may be a chance finding On the other hand it is quite clear that affective disturbances are more frequent as third and fourth symptoms, lending some support to the "common-sense" view that the mental changes follow the physical changes

Constipation appeared as a presenting symptom in Engel's series in 14 of his 32 patients This is very different from the proportion in our series (24 out of 120) which seems to represent the subgroup whose disease started as proctitis or procto-sigmoiditis A more striking feature regarding this symptom is the large number (80) who have not listed it at all

Summary and Conclusion

A method of inquiry into the presenting symptoms of ulcerative colitis is described, making use of an association of patients known as the Ileostomy Association

Diarrhœa as an initial symptom is only slightly more common than bleeding There is little evidence therefore to support existing psychosomatic hypotheses of the origin of the disease

Anxiety and depression are commoner after than before diarrhœa and bleeding

This inquiry could not have been made without the fullest cooperation of the Midland Ileostomy Association, and we should like to record our sincerest thanks to the members, and to all those surgeons who kindly answered our inquiry regarding diagnosis of their patients

REFERENCES

Alexander, F (1952) Psychosomatic Medicine London
Craddock, C C (1953) *Psychosom Med* 15, 513
Daniels, G E (1942) *New Engl J Med* 226, 178
Engel, G L (1954a) *Amer J Med* 16, 416
— (1954b) *Psychosom Med* 16, 496
— (1955) *Amer J Med* 19 231
Grace, W J, Wolf, S, Wolff, H G (1951) The Human Colon London
Groen, J (1947) *Psychosom Med* 9, 151
Halliday, J L (1943) *Lancet*, ii, 692
Hogben, L, Sim, M (1953) *Brit J prev soc Med* 7, 163
Karush, A, Daniels G (1953) *Psychosom Med* 15 140
Lindemann E (1945) *Arch Neurol Psychiat* 53, 322
Paulley, J W (1956) *Lancet*, ii, 215
Sullivan, A J, Chandler, C A (1932) *Yale J Biol Med* 4, 779
— (1935) *Amer J dig Dis* 2, 651
Wittkower E (1938) *Brit med J* ii, 1356

Preliminary Communications

MULTIPLICATION OF RAT-LEPROSY BACILLI IN CULTURES OF RAT FIBROBLASTS

FOR many years experimental rat leprosy has been studied as a model of the human disease. Both are chronic infections caused by mycobacteria in which the bacilli exist as obligate intracellular parasites of mononuclear cells. Until recently neither causative organism has been cultured. Because of the intracellular existence of the bacilli in vivo our attempts to grow rat-leprosy bacilli (*Mycobacterium lepræmurium*) have been made using tissue cultures.

Rees and Wong[1] have recently reported from these laboratories that significant though limited multiplication of *Myco. lepræmurium* can occur in cultures of spleen tissue obtained from previously infected animals. Substantially similar results in spleen cells have been reported by Wallace and his colleagues[2]. Suggestive evidence of multiplication has also been obtained by Hawking[3] using rat monocytes. The successful demonstration, for the first time, of unequivocal multiplication of *Myco. lepræmurium* in tissue culture has been greatly facilitated by the development and use of precise methods for determining the total number of bacilli present in the cell cultures before and after cultivation.[1,2] Previous methods of detecting multiplication, which have depended on the distribution of bacilli in tissue cells, are open to serious error because of the redistribution of bacilli that inevitably occurs in a changing and often diminishing cell population.

Undoubtedly primary cultures of explanted tissue from previously infected animals offer the greatest chance of success, because the bacilli remain undisturbed in the specific host cells. On the other hand such cultures cannot be maintained in a healthy state for the long-term studies required to obtain continuous multiplication of a slowly growing organism like *Myco. lepræmurium* (mean generation time 13 days[4,5]). Such studies require the use of an established line of cells that can be infected with bacilli in vitro. We first tried Earle's L strain of mouse fibroblasts, and, although these cells can be successfully parasitised by *Myco. lepræmurium* in vitro, no multiplication of bacilli was observed in cultures maintained for 46 days. Wallace et al.[2] found the same with L-strain cell cultures, but when the metabolism of these cells was modified by the addition of high concentrations of hydrocortisone limited multiplication of bacilli resulted. It has been our experience that the concentration of hydrocortisone used severely damages the cells, and that the conditions are therefore unsuitable for obtaining continuous multiplication of bacilli.

We have now successfully initiated multiplication of *Myco. lepræmurium* in a strain of rat fibroblast cells without hydrocortisone.

METHODS

Partially purified suspensions of *Myco. lepræmurium* in 5% albumin in saline or in 5% albumin and 5% yeast supplement in phosphate buffer, were freshly prepared for each experiment from the livers of mice infected intravenously 8–12 weeks previously. The suspensions were adjusted to contain approximately 5×10^{10} bacilli per ml. All procedures were carried out in the cold (2–4°C).

Cultures of the 14pf strain of rat fibroblasts[6,7] were maintained in medium containing 50% human cord serum, HCS$_{50}$, and 50% Hanks balanced salt solution, BSS$_{50}$, or HCS$_{50}$ BSS$_{50}$. For each experiment cultures of cells were grown for 7–10 days in 'Pyrex' feeding-bottles, in medium containing only 25 units penicillin per ml and no streptomycin. The medium was withdrawn and the cells carefully washed with an excess of BSS to remove free serum. The cells were then infected by adding to each bottle approximately 10^9 freshly prepared bacilli suspended in 0·0125% albumin in BSS and incubating at 37°C for 24 hours.

Under these conditions the cells remained healthy and readily ingested bacilli which were not directly exposed to the possible toxic effect of serum[8]. On an average approximately 90% of the cells were infected with bacilli as follows: 1–2 bacilli, 15%; 3–5 bacilli, 22%; 6–10 bacilli, 21%; and over 10 bacilli, 31%.

The infected cultures were trypsinised and the cells thoroughly washed in BSS to remove the extracellular bacilli. The cells, after centrifuging, were resuspended in medium (usually HCS$_{50}$ BSS$_{50}$ and 25 units penicillin), carefully maintained in suspension by agitation and rapidly distributed in 1 ml. samples containing approximately 10^5 cells, into pyrex culture tubes. In most of the experiments the tubes were divided into two groups: (a) no addition of antileprous drugs, and (b) addition of 100 γ streptomycin and 0·1 γ isoniazid—a combination expected from chemotherapeutic observations of rat leprosy[9,10] to inhibit growth of organisms in vitro, and so serve as an essential control. Before incubating the cultures at 34 or 37°C, three tubes were set aside for counting the total number of bacilli per tube. The medium was changed every 11 days and retained for counting. Any serious fall in pH or deterioration in the quality of the cells was rectified by the addition of drop quantities of 1·4% sodium bicarbonate or chick-embryo extract, respectively. Three tubes were set aside from each group for counting bacilli on day 13, 26, and 39.

To count accurately the total number of bacilli present in each culture it was first necessary to release completely the bacilli from the cells and so obtain a well-dispersed suspension of organisms. This was achieved in a single operation by exposing the culture tubes to ultrasonic vibration for 15 sec. (Mullard ultrasonic generator type E 7562, frequency 340 Kc. per sec., power 200 watts), a procedure that has been shown to disrupt the cells completely without damage to the intracellular bacilli[11]. Using a modified Breed technique,[12] smears were prepared from a known volume of the disrupted cell cultures, spread over a standard area on a microscope slide and stained by a modified Ziehl-Neelsen method. A count was made of acid-fast bacilli present in equivalent standard samples from each culture. Successive fluid changes from each culture were pooled and counted after similar treatment.

RESULTS

The results of the counts obtained from 9 experiments are shown in the table.

MEAN NUMBER OF ACID-FAST BACILLI COUNTED IN STANDARD SAMPLES FROM CULTURES

Experiment	Group	No. of bacilli				Maximum increase (ratio)
		Day				
		0	13	26	39	
159	A	30·0	66·5	62·0	—	2·2
	B+0·1 mg. HC per ml.		61·5	62·5	—	2·1
162	A	30·7	60·5	58·0	65·0	2·2
	B+0·1 mg. HC per ml.		42·0	45·0	42·0	1·4
164	A	48·3	51·0	55·5	47·0	1·2
	B+0·05 mg. HC per ml.		43·5	53·5	50·0	1·0
167	A	5·8	11·0	19·8	30·5	5·3
	B+0·05 mg. HC per ml.		9·0	23·5	31·5	5·5
170	A	55·0	100·0	98·0	108·0	2·0
	B+100γ SM+0·1γ INH per ml.		62·5	54·0	58·0	1·1
172	A	12·3	29·5	32·0	53·5	4·4
	B+100γ SM+0·1γ INH per ml.		19·5	15·5	13·0	1·6
179	A	32·0	62·6	59·6	—	2·0
	B+100γ SM+0·1γ INH per ml.		30·1	34·5	—	1·1
181	A	9·8	21·6	24·4	—	2·5
	B+100γ SM+0·1γ INH per ml.		14·5	12·8	—	1·5
183	A	10·5	18·5	29·3	32·8	3·1
	B+100γ SM+0·1γ INH per ml.		14·3	13·0	11·6	1·4

HC = hydrocortisone (free alcohol) SM = streptomycin INH = isoniazid

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[1] Rees, R. J. W., Wong, P. C., *Nature, Lond.*, 1958 181, 359.

[2] Wallace, J. H., Elek, S. D., Hanks, J. H., *Proc. Soc. exp. Biol., N.Y.*, 1958 97, 101.

[3] Hawking, F., *Leprosy Rev.*, 1958, 29, 71.

[4] Rees, R. J. W., *Amer. Rev. Tuberc.*, 1957, 76, 915.

[5] Rees, R. J. W., *East Afr. med. J.*, 1957, 34, 361.

[6] Gey, G. O., Hanks, J. H., Barrett, R., *Growth*, 1948, 12, 69.

[7] Ehrmann, R. L., Gey, G. O., *J. Nat. Canc. Inst.*, 1953, 13, 1099.

[8] Hanks, J. H., Gray, G. T., *Int. J. Leprosy*, 1954, 22, 147.

[9] Goulding, R., Robson, J. M., Rees, R. J. W., *Lancet*, 1953, i, 423.

[10] Chang, Y. T., *Int. J. Leprosy*, 1956, 24, 307.

[11] Rees, R. J. W., 1957, unpublished.

[12] Hobby, G. L., Hanks, J. H., Donikian, M. A., Backerman, T., *Amer. Rev. Tuberc.*, 1954, 69, 173.

Each mean count of acid-fast bacilli was obtained from a pool of three cultures, from which 2 or 4 spreads were made and each counted in duplicate In 8 out of 9 experiments the results show a significant increase in the number of bacilli present after incubation in the cultures without streptomycin and isoniazid There was no significant increase in the number of bacilli in cultures containing high concentrations of the drugs In 4 experiments a group of cultures containing hydrocortisone was included because of the report[2] that *Myco lepræmurium* only multiplied within L-strain cells in the presence of the hormone From our results it can be seen that hydrocortisone is not essential for the multiplication of bacilli in 14pf cells In general the initial rate of multiplication corresponds closely to that obtained in vivo in the mouse In some experiments multiplication was almost entirely limited to the first 13 days of incubation, whereas in 3 experiments there was a more continuous increase in the number of bacilli recovered from cultures maintained for 39 days In these experiments the bacterial populations increased approximately 5 5, 4 4, and 3 1 fold, representing significantly greater multiplication than has been obtained in spleen cultures or L-strain cells plus hydrocortisone

Although these results are encouraging, the multiplication obtained is either limited to the initial 13-day period of incubation, or, where it has been more continuous, the rate of multiplication has diminished This could be due to a deterioration in the quality of the cells, since the conditions (adopted primarily for accurate enumeration of bacilli) are not those most suited for providing good cell cultures On the other hand the cell type used for growing rat-leprosy bacilli is important because, using identical methods of assessment, multiplication did not occur in mouse monocytes,[1] in L-strain cells (without hydrocortisone), or in monkey-kidney cells[13] Initiation of multiplication of rat-leprosy bacilli in an established and unmodified line of tissue cells offers therefore, for the first time, a reasonable system in which to study the conditions required for continuous multiplication

We wish to record our thanks to Dr G O Gey for supplying the 14pf cultures and we gratefully acknowledge the technical assistance of Mr C V Gibbs and Miss M Collins

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RESPONSE OF THE INFECTED URINARY TRACT TO BACTERIAL PYROGEN

THE difficulty of establishing the diagnosis of chronic pyelonephritis is well known An attempt has therefore been made to diagnose renal infection by a new and very simple method It seemed possible that the infected kidney might be in some way sensitive to parenterally administered bacterial products and that evidence of such sensitivity might be found in the urine

Changes in the excretion-rate of white and non-squamous epithelial cells in the urine after the intravenous injection of a bacterial pyrogen in 6 normal subjects were therefore compared with those in 10 patients in whom the diagnosis of chronic renal infection was regarded as established beyond reasonable doubt

The controls were 6 normal healthy males who gave no history of urinary tract infection at any time The urine of all was free of protein and showed a normal excretion-rate of white and non-squamous epithelial cells

In the 10 patients, the diagnosis of renal infection was made either on histological evidence obtained from renal biopsy, nephrectomy, or necropsy, or on evidence afforded by a combination of the history, or the presence of nitrogen retention in the absence of any other discoverable cause, with the radiological demonstration of nephrolithiasis, deformities of the pelvi-calycine system, or gross deformities of the renal outlines shown by presacral pneumography Some patients, in addition, had infected urines and nearly all had abnormal cell-excretion rates when first seen

METHODS

The rate of urinary cellular excretion was determined by the method of Houghton and Pears[1] Three specimens of urine were collected at hourly intervals before the intravenous injection of 0 007 γ per kg body-weight of 'Pyrexal' (Wander), a purified lipopolysaccharide derived from *Salmonella abortus equi* Four specimens of urine were collected at thirty-minute intervals, starting from the time of collection of the last control specimen The rate of excretion of white and non squamous epithelial cells was determined on each of these seven specimens The deposit obtained from 10 ml of each specimen was stained by Gram's method to demonstrate organisms From all female patients the urine was collected through an indwelling urethral catheter

Clearances of inulin and *p*-aminohippuric acid were determined using a constant-infusion technique Inulin was determined by a modification[2] of Harrison's method[3] and para-aminohippuric acid by the method of Smith et al[4]

Temperatures were taken in the mouth by clinical thermometer

RESULTS

In each of the patients and the controls, the difference between the means of the cellular excretion-rates in the three preinjection periods and the first two postinjection periods were calculated From these differences for each individual, the mean differences for each group were derived and expressed as a percentage of the mean preinjection value for that group The result for the controls was −10 2%, for the patients it was +186 2% The probability of obtaining such a result fortuitously is less than one in a hundred but more than one in a thousand $(0\ 01>\mathrm{P}>0\ 001)$

There appears to be no correlation between the urine flow and the rate of cellular excretion In two patients, inulin and *p*-aminohippuric clearances showed that the excretion-rate of cells in the urine increases without any change occurring in the glomerular filtration-rate or the effective renal plasma flow In all patients, the rise in cellular excretion occurred within thirty minutes, and thus a considerable time before the onset of rigor or fever in some, the excretion-rate fell as the temperature rose Cortisone and aspirin appear to modify profoundly the expected changes in the urinary excretion of cells in all the cases so far studied from this point of view In some patients, bacteria appeared in the urine after the injection of pyrogen when they had been absent before it in other cases, where bacteria were already present, their number increased greatly after the injection

A case of acute focal nephritis, proven by renal biopsy, a case of the nephrotic syndrome, and a case of the malignant phase of essential hypertension, all with initially abnormal urinary cell excretion rates, failed to show any change in their rates after the injection of pyrogen All developed a fever

Work is continuing in an attempt to elucidate the mechanism of this response of the infected kidney to a substance of bacterial origin injected intravenously, and to demonstrate conclusively whether or not it is in fact specific for cases of renal infection At present, it seems permissible to suggest that the phenomenon is one of hypersensitivity of a site of infection to parenterally administered, heterologous bacterial products, and that it thus bears obvious resemblances to that described by Sanarelli[5] and by Shwartzman[6]

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[13] Wong, P C PH D thesis, London University, 1957

[1] Houghton, B J, Pears, M A *Brit med J* 1957, i, 622
[2] Diggins, F W, Sanderson, P H Personal communication
[3] Harrison H E *Proc Soc exp Biol, N Y* 1942, 49, 111
[4] Smith H W, Finkelstein, N, Crawford, B, Graber, M *J clin Invest* 1945, 24, 288

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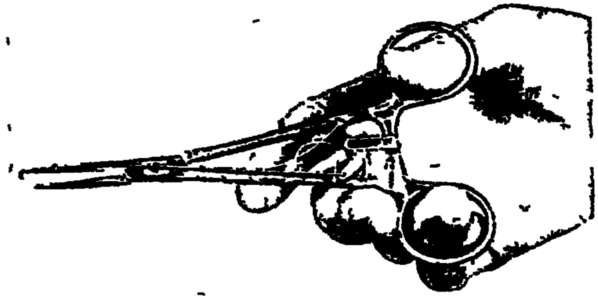
5 Sanarelli, G Ann Inst Pasteur, 1924, 38, 11
6 Shwartzman, G *J exp Med* 1928, 48, 247, *Proc Soc exp Biol N Y* 1928, 26, 207

New Inventions

A PRECISION CLIP APPLICATOR

FOR several years I have been using a silver clip applicator that includes a hook which automatically pulls the vessel into an exact position for occlusion by the limbs of the silver clip The action of the mechanism for primarily drawing the vessel into position is an integral part of the clip applicator and works synchronously with the approximation of the silver clip limbs (see figure) The mechanism is so designed that the hook completes its action, drawing the vessel into position, before the clip has closed more than ten per cent



Precision clip applicator in open position

I have used this clip applicator mostly in occluding major branches of the circle of Willis in order to trap aneurysms It has been used for getting behind aneurysms and drawing their neck into a precise position within the clip The instrument has been found quite useful for holding and clipping the stalk in pituitary-stalk sections or hypophysectomies With it the identification of the stalk and pulling it into position within the silver clip are straightforward

With the usual applicator the clip may not be applied properly unless the vessel is dissected free and lifted away from the brain tissue, or unless the applicator is pressed against the tissue to force the vessel within the clip This instrument has been found useful not only in dissecting out the vessel from the pial and arachnoidal attachments but also in automatically lifting the vessel a millimetre or two away from the tissue surface for precision clipping, the principal contact being with the vessel occluded The instrument has also been found useful for precise clipping in deep small openings where depth perception is difficult. By use of the hook, the vessel can be properly oriented to the clip and mechanically drawn into the proper position for clipping A standard MacKenzie clip-rack can be used by merely grinding off the foot of the rack on the hook side, which allows the hook to drop down so that the tips of the clip applicator can assume their usual position

No serious disadvantages have been found in the use of this clip applicator except that caution must be exercised, as with any surgical instrument, when advancing into or coming away from the wound

I wish to thank Mr J A Jones, machinist, for his assistance in the making of the pilot instrument

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GEORGE W SMITH
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Reviews of Books

Sir Charles Bell

His Life and Times SIR GORDON GORDON-TAYLOR, K.B.E., C.B., F.R.C.S., consulting surgeon, Middlesex Hospital, London, E. W WALLS, M.D., B.SC., F.R.C.S.E., S A Courtauld professor of anatomy, Middlesex Hospital Medical School. Edinburgh E & S Livingstone 1958 Pp 288 42*s*

WITH characteristic vigour, Sir Gordon Gordon-Taylor has chosen to mark his 80th birthday by collaborating with Professor Walls in the production of an erudite and intensely interesting study of their great predecessor at the Middlesex Hospital. When Charles Bell first came to London, in 1804, he was already widely known as the author of two anatomical textbooks Two years later the appearance of his *Essays on the Anatomy of Expression in Painting* revealed him not only as an expert anatomist but also as one possessed of the "most exquisite taste and feeling for sculpture and painting" In due course he was appointed surgeon to the Middlesex Hospital, and published the first of the series of papers upon the structure and function of the nervous system for which he is chiefly remembered today—and round which was waged his unhappy controversy with Magendie of Paris

In any age, Bell would have provided material for a lengthy and valuable biography, but he also lived in a period of great political, military, and intellectual excitement. (When Waterloo was fought, Bell crossed to Brussels and worked among the wounded for three days, with scarcely as many hours' sleep) His contemporaries were such men as Abernethy and Astley Cooper, Syme and Dupuytren, and an important characteristic of this book is the way in which Bell is at all times shown in relation to a carefully detailed background (It is strange, though, that no mention is made of Abraham Colles, who was born the year before Bell, and died a year later Like Bell, he graduated at Edinburgh and, like him, was hospitably received by Astley Cooper when he moved to London.)

A useful appendix of 90 pages includes a reproduction in its entirety of Bell's *Idea of a New Anatomy of the Brain*, and much hitherto unpublished correspondence about him. Appendices usually go unread, but this one, with its notes about the Resurrection Men, the Waterloo casualties, and Bell's first cases of the palsy which perpetuates his name, is likely to engage and reward the reader's interest as much as the fascinating pages which precede it.

High Arterial Pressure

F H SMIRK, M.D., F.R.C.P., F.R.A.C.P., professor of medicine, University of Otago, Dunedin, New Zealand Oxford Blackwell Scientific Publications 1958 Pp 764 75*s*

FOR many years Professor Smirk has studied patients with hypertension, and his wide experience is set out in this comprehensive volume.

In the early chapters he introduces the concept of the "basal blood-pressure", the importance of which becomes increasingly clear later Succeeding chapters are concerned with, inter alia, the natural history of hypertension and the effect of environment on the blood-pressure, and the clinical manifestations of hypertension and the physiology of blood-pressure regulation Experimental hypertension is covered fully, and an excellent chapter on the pathogenesis of high blood-pressure—dangerous ground skilfully negotiated—prefaces the chapter dealing with treatment Professor Smirk assesses all the well-known and several less well-known hypotensive agents and procedures carefully and fairly, though he leaves no doubt as to his own preference for ganglion-blocking agents The management of patients with hypertension is discussed usefully in great detail Precise details of certain aspects of treatment are contained in six appendices, and a seventh covers, with admirable brevity, papers published late in 1956 and in 1957 during the printing of the book.

Professor Smirk has provided from his own experience and from a comprehensive survey of the literature both a work of reference and a book which should be read by all clinicians undertaking the care of patients with high arterial pressure

Tumours of the Soft Somatic Tissues

GEORGE T PACK, M D, LL D, F A C S, attending surgeon, Memorial Center for Cancer and Allied Diseases, IRVING M ARIEL, M D, F A C S, associate clinical professor of surgery and associate attending surgeon, New York Medical College London Cassell 1958 Pp 820 231s

EVERY surgeon, whether he works in a general or a specialised field, encounters from time to time a tumour which causes him more worry and doubt than half a dozen ordinary neoplasms Such a tumour is very often derived from "soft somatic tissues"—fascia, muscles, synovia, blood-vessels, or nerves—and there are several reasons why it poses special problems Sarcomas, synoviomas, and malignant neurilemmomas are rare, and few surgeons can draw on a considerable experience of them, pathologists sometimes give opinions about biopsy specimens at variance with the clinical features, and publications on them are found to consist largely of monographs listing a small number of cases not consistently treated No book at all has previously been published on this important group of tumours as a whole

The present volume, then, meets a real need It represents the experience of a group of internationally famous surgeons, who were for the most part dealing with the unrivalled material of the New York Memorial Center This is essentially a practical manual on the management of actual cases, and the authors are at pains to stress that many factors besides the histogenesis of the tumour must be considered when planning treatment The price may seem rather high But the volume is beautifully produced, and illustrated with five hundred excellent photographs and drawings The surgeon who buys a copy now will derive an unusual and pleasurable sensation from handling a book the title of which is likely to become very familiar in medical literature

Erythroblastosis Fetalis

FRED H ALLEN, JR, M D, clinical associate in pædiatrics, and LOUIS K DIAMOND, M D, associate professor of pædiatrics, Harvard Medical School Boston Little, Brown & Co London J & A Churchill 1958 Pp 143 30s

THIS short book is one of a series of collections of articles on medical progress originally published in the *New England Journal of Medicine*, the articles on which it is largely based were published in October, 1957 The book contains a remarkable amount of information and includes a useful glossary of technical terms A succinct account of the blood-group factors, including rare ones, is given, the mechanism of production of the syndrome is clearly discussed and diagnosis fully dealt with The technique the authors use for exchange transfusion is given in some detail In this country the tests and manœuvres described would all be carried out in the children's department of a hospital, and the finer points of blood-grouping are dealt with by the National Blood Transfusion Service centres Nevertheless all who deal with newborn children will find this book useful, and our only regret is that its price, excessive for this country, will keep it resting on the library shelf instead of in the resident's pocket

Obstetric Practice

H BRUCE WILLIAMS, CH M, F R A C S, F R C O G, lecturer in clinical obstetrics, King George V Hospital and University of Sydney Sydney and London Angus & Robertson 1957 Pp 168 25s

IN his handbook of abnormal obstetric practice (it does not deal with the normal) Mr Williams discusses the diagnosis and treatment of the complications of pregnancy and labour The brevity with which he has chosen to do this has necessitated some sweeping generalisations, for examples, "Endeavour to assess the size and weight of the child, for a very large child cannot be delivered by the vaginal route", "Remember that if you do a vaginal examination and can feel the sacrum, the diagonal conjugate is reduced, and therefore the child of normal size could not be delivered per vias naturales", "The patient may be a multipara with previous normal deliveries of normal sized infants, thus excluding pelvic contraction", and "The causes of fœtal distress during labour are (*a*) short cord, (*b*) prolapse of the cord" For those with little experience of obstetrics, such an approach is seldom suitable The classifications would not all meet with general favour thus the causes of habitual premature interruption of pregnancy are given as (1) diseased cervix, (2) no apparent cause, (3) other causes which are not diagnosed; and the causes of inversion of the uterus are grouped as (1) incorrect management of the third stage of labour, (2) spontaneous inversion, for example (i) pressure on the fundus of an atonic uterus or (ii) pulling on the cord

Although there is much that is interesting in Mr Williams' many original views, his book is unlikely to commend itself to teachers who favour a more orthodox text for their students

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The Tissues of the Body (4th ed London Oxford University Press 1958 Pp 415 40s)—It is not quite twenty years since Prof W E Le Gros Clark's book first appeared, yet it can already be counted one of the classic texts of anatomy In this new edition he has pursued his policy of bringing to the notice of his students not only the tried principles and generalities of the subject but also some frequent glimpses of "the advancing front of scientific adventure" It is for this reason that this book is by far the best introduction to the study of anatomy It educates, stimulates, and evokes the critical spirit proper to youth Few anatomists of today could claim such a wide and up-to-date acquaintance with the multifarious activities of their fellows as can Professor Le Gros Clark His book is, indeed, not merely a superb introduction for the novice in anatomy, but almost equally valuable to the professional as a periodic review of progress in the subject

Clinical Heart Disease (5th ed London W B Saunders 1958 Pp 673 66s 6d)—This excellent book by Prof Samuel A Levine, of Harvard, has expanded greatly since it was first written in 1936, but it has remained a great favourite both with medical students and physicians It was practical, clinical, eminently readable, and not too long Unfortunately, it had lately become out of date, and it is a pleasure to find that this has now been remedied Two sections have been added, both by well-known authors and both excellent One is on congenital heart-disease by Dr Alexander Nadas, cardiologist to the Children's Hospital at Boston and himself the author of a well-known book on congenital heart-disease His section is of only 32 pages, which seems small in a volume which has now been expanded to 673 pages, but that is perhaps the correct proportion for the adult cardiologist. The lack of illustrations in this section is disappointing, but it is in keeping with the rest of the book, except for the section on electrocardiography In this large section by Dr Harold Levine, who is in charge of electrocardiography at the Peter Bent Brigham Hospital, vectorcardiograms are shown and described with the electrocardiograms, but are difficult to "read" and are not married with the description of the electrocardiograms, as perhaps they should be in a textbook of this sort This is not the right book for those who like the physiological approach It is poor on the venous pulse, and auscultation sometimes does not receive the emphasis that one would expect from Professor Levine, especially in the section on acute rheumatic carditis Nevertheless the text can be read and enjoyed, and remembered by its good clinical sense and anecdotes in a way that is most unusual in a specialised monograph

Spinal Anesthesia (Springfield, Illinois Charles C Thomas Oxford Blackwell Scientific Publications 1958 Pp 61 22s 6*d*)—Prof John B Dillon, of the University of California Medical Center, here presents a very concise account of the essential practical facts concerning spinal anæsthesia He has written it for residents in anæsthesia and for those who practise spinal anæsthesia but who have had neither the time nor the opportunity to explore some of its aspects He provides a useful introduction for residents, but the book is unlikely to appeal to those who practise anæsthesia, because it does not attempt to appraise deeply the physiological and pathological implications of the technique

THE LANCET

LONDON 19 JULY 1958

Bacterial Endocarditis

BEFORE the introduction of chemotherapy bacterial endocarditis was almost invariably fatal, but even today probably one in every four patients succumbs FRIEDBERG[1] has shown that this is due mainly to delay in treatment arising from errors in diagnosis, and to the inadequate treatment of patients with resistant organisms Patients over the age of 40 and those with persistently negative blood-cultures[2] have an appreciably greater mortality Treatment should be started at the earliest suspicion—unexplained fever, anæmia, splenic enlargement, or changing murmurs, accompanying a cardiac lesion Eradication of organisms deeply buried in vegetations depends on their being reached by adequate concentrations of an antibiotic to which they are sensitive, and as host defence mechanisms are virtually impotent in these situations, the antibiotic must be bactericidal rather than bacteriostatic[3] EAGLE et al[4] have shown in experimental lesions that the rate of destruction of organisms by penicillin depends on their susceptibility and the total time that an effective concentration is maintained at the site of infection, the greater the number of organisms, the longer must be the treatment EAGLE et al[5] also deduced that in their experiments a serum level five to twenty times the minimum inhibitory level in vitro was required, and it is likely that even higher levels are required in bacterial endocarditis to ensure diffusion into the vegetations Such levels cannot be attained with depot preparations The failure of penicillin in adequate doses to cure some patients, even though the organisms are sensitive, may be the result of a heavy concentration of organisms in the vegetation[4], in these conditions organisms multiply only very slowly, and accordingly penicillin is largely ineffective The combination of penicillin with streptomycin has been shown in vitro by HUNTER[6] to overcome this difficulty, such a combination is highly bactericidal

FINLAND[7] has recently reviewed the present position regarding treatment Whenever possible the organism should be isolated, but there is little advantage in taking blood-cultures for longer than forty-eight hours since GRIFFITH and LEVINSON[8] found that 98% of positive results were obtained in this time Treatment should be started during incubation of the cultures, and the choice of antibiotic depends upon the probable organism Almost any organism can cause the disease, but *Streptococcus viridans* is easily the commonest, enterococci are more likely after genitourinary operations, and staphylococci after cardiac surgery FINLAND recommends penicillin whenever the organism is highly or moderately sensitive, but streptomycin should be added if more than 0 2 unit per ml is required for inhibition in vitro, and in all enterococcal infections None of the tetracyclines or chloramphenicol should ever be used alone where gram-positive organisms have been isolated, even when these are sensitive in vitro and despite occasional reports of cure, negative blood-cultures and clinical improvement may usually be obtained, but relapse almost always follows Streptomycin and erythromycin must never be given alone, for fear of resistance developing, and sulphonamides seem to have no place Short courses of treatment have been tried, particularly in the U S.A , and HUNTER and PATERSON[9] have reported a relapse-rate of only 6% in 146 patients treated for fourteen days with up to 12 million units of penicillin and 2 g streptomycin daily TOMPSETT et al[10] found that 24 patients out of 35 were cured after a similar period by 6 million units of penicillin and 1 g streptomycin daily, they regarded a further 8 as "probable cures" KELLOW and DOWLING[11] claim that a course of only ten days is necessary in infections with streptococci inhibited by 0 5 unit per ml ; but this hardly accords with general experience, and FINLAND prefers the recommendations of HUNTER and PATERSON Thus, when the organism is a highly sensitive streptococcus, inhibited by 0 1 unit per ml or less, a fourteen-day course may be given consisting of 2 million units of penicillin daily combined with 2 g streptomycin daily in the first week and 1 g streptomycin daily in the second Organisms sensitive to 0 2 unit per ml require 8 million units daily for two weeks followed by 4 million units daily for three weeks, combined with 1 g streptomycin daily If the organism is only sensitive to 1 unit per ml or more, the course should be 12 million units daily for three weeks and subsequently 4 million units for four weeks streptomycin 1 g daily is given throughout, and probenecid 0 5 g six-hourly is added to enhance penicillin blood-levels Isolation of an enterococcus demands this last programme as a minimum, and if the organism is relatively insensitive, up to 20 million units of penicillin daily is advisable, administered if necessary by constant intravenous infusion Staphylococci sensitive to 1 unit per ml are best dealt with by administering 12 million units of penicillin daily combined with probenecid for six weeks, and more resistant staphylococci must be treated simultaneously with two antibiotics to which the organism has been found moderately or highly sensitive Such combinations might be erythromycin or novobiocin with streptomycin, chloramphenicol, or a tetracycline, or chloramphenicol with streptomycin Bacitracin may be needed if the position is desperate. Probenecid blocks the excretion of penicillin only and is useless with other antibiotics For less common organisms, treatment can be planned only in the light of known sensitivity

Such recommendations may seem complex, but inadequate or misdirected treatment, while inducing a temporary quiescent phase, may also induce resistance in the infecting organism, and thus make ultimate eradication more difficult Early diagnosis or, preferably, prophylaxis [12] offers the best prospect If any doubt exists it is only prudent to prescribe the longer course, and in every case unremitting watch must be kept for any sign of relapse

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[1] Friedberg, C K *J Amer med Ass* 1950, 144, 527
[2] Cates J E, Christie, R V *Quart J Med* 1951, 20, 93
[3] Garrod L P *Brit med J* 1953, ii, 953
[4] Eagle H , Fleischman, R., Musselman, A D *Amer J Med* 1950, 9, 280
[5] Eagle H Fleischman, R., Levy M *New Engl J Med* 1953, 248, 481
[6] Hunter, T H *J Amer med Ass* 1950, 144, 524
[7] Finland, M *ibid* 1958, 166 364
[8] Griffith, G C , Levinson, D C *Calif Med* 1949, 71, 403
[9] Hunter, T H , Paterson, P Y in Disease a Month series, 1956 Chicago
[10] Tompsett R., Robbins, W C , Bernsten, C *Amer J Med* 1958, 24, 57
[11] Kellow, W F , Dowling, H F *Arch intern Med* 1957, 100, 322

Bone-marrow Transplantation in Blood Diseases

LAST year we drew attention to experimental work on the transplanting of bone-marrow to animals whose own marrow had been inactivated by exposure to radiation [13] These experiments had shown that, if suspensions of bone-marrow cells from healthy animals are injected intravenously into the irradiated animals, not only do a large proportion of the latter survive an otherwise fatal dose of irradiation, but also there is evidence that the donor cells proliferate in the host's marrow This discovery had been applied to the therapy of animals with transmitted leukæmia, they were exposed to a dose of X-radiation sufficient to destroy the bone-marrow, and then normal marrow cells were given, in some cases proliferating donor marrow replaced the former leukæmic marrow and the animals survived for some time The possibility of transplanting healthy marrow to patients with blood diseases has been explored with great energy The technique should be applicable to patients who have aplastic anæmia, or whose marrow has been rendered aplastic by exposure to radiation or by drugs such as nitrogen mustard or busulphan ('Myleran') given for the treatment of leukæmia, Hodgkin's disease, or similar conditions, or in an attempt to relieve the symptoms of malignant tumours Last October a conference on these matters was held at Boston, Mass , under the general chairmanship of Dr SHIELDS WARREN and Dr WILLIAM DAMESHEK, and the proceedings have been reported in *Blood* [14]

In the first session sources of bone-marrow and techniques for its preservation and administration were discussed L M TOCANTINS used ribs removed at thoracotomy operations, and he could get 10–15 specimens weekly, a 7–8 in length of rib yielded 6×10^8 to 6×10^9 cells, but he pointed out that, since adult cells are of little value to the recipient, the differential count should be known He also used marrow obtained from the vertebræ of cadavers, removed with sterile precautions within two hours after death WILLIAM MCFARLAND obtained marrow by aspiration from the posterior ilium with a Bierman needle [15], the marrow was aspirated into heparinised saline, and $1\text{–}4 \times 10^9$ nucleated cells were obtained from a single donor He also used cadaver marrow obtained from the sternum as well as the vertebræ E D THOMAS preferred marrow from fœtal sources when possible, $2\text{–}4 \times 10^9$ cells are obtainable from the four long bones, he forced the marrow through graded stainless-steel meshes [16] to obtain an even suspension of cells W H CROSBY and J AKEROYD had used whole-rib transplants, in these transplants the rib bone disappears and is replaced by fibrous tissue, and marrow later regrows within this fibrous tissue The bone-marrow suspension obtained from these various sources either has been given within three hours after preparation or has been preserved in glycerin by the Polge technique and stored at −70 to −80°C

The second session was devoted to the immunological difficulties when donor tissues are given to hosts that are not identical—difficulties that have often proved a bar to long-term survival C C CONGDON stated the problem shortly Normally mice live for 29–35 months, after lethal irradiation they die within ten days, but if given injections of healthy bone-marrow they survive and apparently recover But thirty to ninety days after irradiation followed by marrow treatment they begin to die, and all are dead by nine to ten months after exposure This late fatality is an immune reaction due to the presence of foreign bone-marrow T MAKINODAN recalled that mice given lethal irradiation can be protected by either mouse marrow or rat marrow, which proliferates under these circumstances [13] With rat marrow the late death-rate was increased and the animals showed a syndrome of loss of body-weight, increase of beta and gamma serum-globulins, and slow reaction to introduced antigens MAKINODAN suggested that there were good reasons for supposing that the late deaths were due to reactions of the host to the transplant, and therefore the amount of marrow injected should be kept to the minimum and as much extraneous tissue as possible should be removed J J TRENTIN pointed out that marrow used in these protection experiments can be autologous, isologous (same genotype as the recipient), homologous (same species but different genotype), or heterologous (e g , rat into mouse) The late-mortality disease occurs in mice protected with homologous or heterologous marrow, but not when isologous or autologous marrow The "heterologous disease" is more severe than the "homologous disease", and the homologous disease is worse with certain kinds of genotype incompatibility TRENTIN, unlike MAKINODAN, believes that the late fatality is due to reaction of the *donor* tissue, probably the transplanted lymphoid elements, against the tissue antigens of the otherwise tolerant host, and he points out that there is no secondary hæmopoietic depression and that skin grafts from the marrow donor into the host will persist TRENTIN also drew attention to an earlier type of mortality when high but sublethal doses of irradiation were followed by a dose of homologous marrow of the order needed to protect against lethal irradiation This earlier mortality is associated with secondary hæmopoietic depression and appears to be related to the ability of the host to reject transplanted homologous marrow—a sort of reaction that may well be observed in the clinical application of marrow transplantation

In the third session clinical results were discussed MCFARLAND reported on 6 cases of aplastic anæmia cared for by DAMESHEK's group Bone-marrow from posterior ilium was obtained from donors whose blood type was as near as possible to that of the recipient Each patient received one to three infusions a day for five to seven days, this meant using for each patient marrow from eight to twelve donors and taking between $0\;95 \times 10^{9}$ and 2×10^{9} cells per donor In one later case only one donor was used, large amounts of marrow being obtained from both posterior ilia Large doses of corticosteroids were given in order to reduce the immune reactions So far encouraging results have been obtained in all the patients Atkinson of Philadelphia mentioned the case of a child with acute leukæmia who was treated with radiation followed by marrow infusion, the donor being the patient's identical twin The child, who was also given corticosteroids before and during therapy, was " packed in rice and rotated to give equal exposure The entrance dose was calculated to be 400r and the exit dose 240r " The irradiation made the child very ill, and she was nearly dying when given an infusion of $2\;65 \times 10^{9}$ marrow cells In twenty-four hours the clinical condition was much improved, and in two weeks there was evidence of a remission, unfortunately this did not last long Kretchmer of Oak Ridge reported results with 2 cases of leukæmia which had relapsed after prednisolone treatment, the patients were given X rays followed by marrow infusion, and were very ill afterwards In 1 patient the marrow was obtained from the patient's mother, who had a different minor group antigen, several infusions were given The patient eventually improved somewhat, and some months later there was still evidence that donor cells were present Earlier, Tocantins had reported results of marrow infusions in 7 leukæmic patients whose own marrow had become hypoplastic after chemotherapy 2 patients had " notable cellular responses " He also mentioned a 16-year-old patient with terminal leukæmia and a low bone-marrow count who was given 150r total body irradiation followed two days later by marrow transfusions containing $5\;4 \times 10^{9}$ nucleated cells, there was a complete clinical and marrow remission which had persisted for four months at the time of the report

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[12] Wedgwood J *Lancet*, 1957, ii, 922
[13] *Lancet*, 1957, ii, 127
[14] *Blood*, 1958, 13, p 288 et seq
[15] Bierman, H R , Kelly, K H *ibid* 1956, 11, 370
[16] Thomas, E D *ibid* 1955, 10, 600

A fourth session dealt with chemical compounds that protect bone-marrow from radiation, an aminoethylthicuronium compound was shown to enable larger doses of irradiation to be given safely to mice with localised lymphomas, with correspondingly greater reduction in the size of the tumours

Summarising, the report states that practical problems of obtaining, preserving, and administering marrow can all be worked out. But

> " the big ' catch ' in the whole thing was the immunologic reaction How could this be handled ? As yet no good technics had been evolved and it was probably best to proceed with the transplantation technics, learn as much as possible about them, and hope that tolerance for introduced marrow might be established and that anti-immune methods might be worked out Whether or not attempted destruction of leukæmic tissue (and normal marrow) followed by attempts at marrow repopulation had some chance of being successful remained to be seen At this writing, it seemed doubtful, not only because the leukemic tissue (or the proliferating stimulus) could not easily be overcome by radiation, but because the immunologic process was probably resistant to the doses of radiation that could be used in the human without fatality "

Heller and Yakulis[17] have lately described the case of a man with Hodgkin's disease whose marrow had become aplastic after the administration of tretamine (T.E.M.) He was given an intravenous injection of marrow pooled from four suitable donors The patient's genotype was O, M, CDe/cDe, four of the donors were N-positive and two were E-positive The treatment was followed by recovery, and N and E erythrocytes were still detectable in the peripheral blood ninety-eight days after the infusion, after that they declined and none of these foreign cells could be found a hundred and forty days later Heller and Yakulis remark that so far few similar reports have appeared This is true enough Thomas et al[18] reported 6 cases in September, 1957, their results were not impressive, a temporary " take " of the marrow transplant being found in only 2, but some of their patients were very ill and 3 died within fifty days from their primary disease Humble and Newton[19] gave marrow to 5 patients, but they were concerned only to show that such infusions were technically possible and had no immediate ill effects The reason for the paucity of reports may be found in the difficulties that were discussed at the Boston conference, and it is clear that marrow infusion is not a treatment to be lightly undertaken Ferrebee[20] estimates that from 2×10^{9} to 20×10^{9} nucleated marrow cells are needed for repopulation of the marrow space of a man But these reports show that, despite discouragements, the possibility of using marrow transplantation is being carefully studied, and already hopeful results have been obtained in aplastic anæmia

Preventable

This is the time of year when messages come from tankers in the Persian Gulf saying that some member of the crew is ill, or has died, from the effects of heat. The deaths may not be many, but they are very distressing, for the person who dies is usually a young man who a few days previously was in ordinary health In their paper this week Dr Leithead and his colleagues give a clear account of heat illness as seen when the patients are landed at an oil-town in Kuwait, and they explain where the dangers lie We earnestly hope that, with this additional evidence before them, the shipowners and Government authorities concerned will consider what more can be done to stop these unnecessary and tragically useless deaths

Of course a great deal has been done already Many tankers have cooling systems for messrooms and sick-bays, some now have air-conditioning of living quarters, and all must fulfil conditions of heat insulation laid down by the Ministry of Transport None, however, have yet achieved the special system of " tropicalisation " used in the Royal Navy Though amenities have so much improved, the short voyages from this country to the Gulf ports can still put a big strain on human adaptability to contrast After exposure to the coolness of an English summer, the crew may have hardly begun to adjust to heat before it strikes them (" like a sword ", as T E Lawrence said) when they leave the Suez Canal

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[17] Heller, P , Yakulis, V *Lancet*, 1958, i, 1131

[18] Thomas, E. D , Lochte, H L Jr , Wan Ling Chu, Ferrebee, J W *New Engl J Med* 1957, 257, 491

[19] Humble, J G , Newton, K A *Lancet*, 1958, i, 142

[20] Ferrebee, J W *Blood*, 1958, 13, 273

On each voyage, acclimatisation must be achieved almost afresh, and there is a danger period, of a week or more, until the body has learnt to conserve salt by reducing the salt content of the sweat

Young men are casual, and a certain foolhardiness befits seafarers But these are poor consolations after a man has died because he did not bother to take extra salt at meals, or thought the suggestion soft Surely, people who make use of scientific discoveries, and live the new kind of lives that science has made possible, ought to be willing to listen also to what science says about the preservation of their health and safety in the new artificial environments? But the necessary knowledge needs to be supplied to them repeatedly and with conviction, and, though many senior officers are interested, they mostly lack time for promoting preventive medicine in detail Of course, if the ship has a doctor, he will be able to overcome irrelevant prejudices and make the crew understand that salt deficiency is something which anyone but a fool will take trouble to avoid But ships with fewer than 100 people on board do not have to carry a doctor

Dr Leithead and his colleagues suggest various ways in which the risks of these voyages could be reduced But there is another that leaps to the eye Granted that one cannot expect to have a fully qualified medical man in every vessel at sea, *why should there be this immense* difference between the medical care of 101 men, who *must* have a registered medical practitioner, and of 99 who need have nobody trained to advise them or attend wisely to those minor illnesses which in the tropics are so uncomfortably liable to become major? Many years have now passed since the Association of Sea and Air Port Health Authorities recommended that the smaller ships should each carry a sickbay steward We must *ask why this is not yet done*

Annotations

ORIGINS OF SOCIAL PSYCHIATRY

It is commonly believed that a real increase in mental breakdown is following on the raised tempo of modern life and our rapid cultural changes Unfortunately the statistics are still so fallible, and the boundaries of mental health and illness so hazy, that fact can scarcely be distinguished from fallacy—let alone from fantasy Some aspects of the "horizontal" approach, as it were, to culture and mental illness by G M Carstairs in his anthropological work were lately reviewed in these columns[1], and on July 8 at the Institute of Psychiatry, London, Prof George Rosen, of Columbia University, presented a "vertical" or longitudinal view

In a scholarly address he pointed out that the concept of sociocultural determination in mental illness is not by any means new Benjamin Rush studied the effects of the American Revolution on the participants being an ardent revolutionary himself, he noticed among his ranks an increase in health and happiness, the cure of hysterical disorders among the women, and blessings granted to previously infertile marriages Among those still loyal to the British, however, mental and physical breakdowns were common, and a particular type of hypochondriasis ("protection fever") was described After the peace of 1783, unwonted freedom led to a further form of insanity called by him "anarchia" Although French writers had noted mental accompaniments to their revolution, it seemed that Rush (though not entirely unbiased) could be credited with one of the *earliest attempts to establish a* causal correlation between social upheaval and mental *consequence*

This concept, as Professor Rosen explained, spread widely during the next century, and Rudolf Virchow in 1848 put forward a theory of "epidemic psychoses" indicative, he said, of major disturbances in man's life, and he distinguished between "artificial" (i e, social) and "natural" phenomena In the following year he carried the idea further, suggesting that mental and physical epidemics came and went at the turning-points of civilisation and could give us insight into the popular feelings of the time, but Griesinger regarded political change as an aggravating factor rather than a cause At about the middle of the 19th century the concept of the "rising tide of madness" came to the fore, and it was slightly comforting to realise that the pessimists of today were the descendants of such a long line of Jeremiahs On the positive side, a consequence of these views was an attack on the social structure itself with the aim of lessening the stresses therein Hawkes in 1857 argued for wide and enlightened social reforms Towards the end of the century a number of workers tried to provide a better factual basis by studying the incidence of insanity in different places and at different times, much evidence was in conflict, but the work of Durkheim on suicide was outstanding Unfortunately the great discoveries in pathology and bacteriology overshadowed this work, although interest in it was now active

Regarding future work, Professor Rosen concluded that certain social variables, such as wars, epidemics, or slumps, should be defined and studied at sociological, psychiatric, and physiological levels, and along the time axis He hoped that the historian, by clarifying issues in terms of their backgrounds and showing linkages not readily apparent, could make some contribution to the multidisciplinary approach Few would disagree with him

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[1] *Lancet*, 1958, i, 419

CONGENITAL MALFORMATIONS

It has been apparent for many years that the best way to study associations between events in the early months of pregnancy and congenital malformations is prospectively To go back into the pregnancy history after the birth of the malformed child is, in general, unsatisfactory, unless the investigation is carefully controlled This method led to an overestimate of the risk to the fœtus after rubella, Hill et al[1] now estimate from prospective studies that the risk of major defect is 50% in the first month, 25% in the second, and 17% in the third They suggest, however, that the risk may vary from year to year and between one country and another With careful controls, Stewart et al[2] have used the retrospective method more successfully in relation to malignant disease in childhood

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[1] Hill, A B, Doll, R, Galloway, T McL, Hodges, J P W *Brit J prev soc Med* 1958, 12, 1

[2] Stewart, A, Webb, J, Hewitt, D *Brit med J* 1958, i, 1495

One method of conducting a prospective inquiry is to use the records of maternity hospitals, listing the incidents recorded in pregnancy and then noting the result of the pregnancy. Carter[3] reported a study of this kind on about 15,000 deliveries in a London maternity hospital and found that none of the commonly recorded events in pregnancy were followed by a significant increase in the rate of malformation. There was a suggestion, however, that the rate might be higher after threatened abortion; and Turnbull and Walker[4] have since also found, though again not at a high level of significance, a greater rate after threatened abortions. Hospital records, while satisfactory for such items as mother's age and parity, inevitably give incomplete information about events early in pregnancy. The ideal is for a single trained observer to make special inquiry of the mother about the third month in pregnancy, and for this observer then to await the result of the pregnancy. The first general prospective study of this kind has now been reported by Dr Alison McDonald.[5]

McDonald interviewed 3295 mothers at the time of booking—this was mostly in the fourth or fifth month of pregnancy—at the Watford and St Albans clinics in 1952–55. She was able to discover the outcome of 3216 of these pregnancies. There were 72 miscarriages and 63 stillbirths. Nearly all the surviving infants were examined by doctors and the majority by a pædiatrician. Necropsies were performed on all but 8 of the stillborn and all but 4 of the 35 infants who died neonatally.

Major malformations were found in 50 (1·5%) and minor malformations in 72 (2·3%). These rates agree well with those in other series of booked cases (hospital series including emergency admissions naturally show a higher rate) in which the children are not followed beyond the neonatal period. For the minor malformations there was no association with any event early in pregnancy. This was true, too, for the major malformations and threatened abortions, extramarital conception, injury, fainting, uterine retroversion, rhesus incompatibility, marked anxiety, and emotional shock. The mothers of the children with major malformations had an above-average incidence in early pregnancy of fairly heavy work, acute febrile illness, active or quiescent pulmonary tuberculosis, and anæmia. Inevitably the number of mothers affected in these ways was small and the associations do not reach high levels of significance. It is noteworthy that the 6 mothers who had a specific fever early in pregnancy (pertussis in 2, mumps in 2, rubella in 1, infectious hepatitis in 1) all had normal babies.

This survey shows how far we are from having any idea of the cause of most congenital malformations. It is known that relatively few are essentially genetically determined, though for many there is evidence of genetic predisposition. Environmental factors must be playing some part in the causation of most malformations, but none of the common events in pregnancy, and only rubella and toxoplasmosis among rare events, have been convincingly incriminated. There has been much more success in relating certain common malformations to social class, maternal age, birth-order, geography, and season of the year. These, however, afford only indirect clues, and the primary environmental factors concerned in most malformations remain unknown.

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[3] Carter, C. O. J. Obstet. Gynæc., Brit. Emp. 1950, 57, 897.
[4] Turnbull, E. P., Walker, J. ibid. 1956, 63, 553.
[5] McDonald, A. D. New Engl. J. Med. 1958, 258, 767.

CHRONIC IDIOPATHIC JAUNDICE

In 1954,[1] under the title a New Liver Disease, we drew attention to an apparently rare disorder of the liver reported independently by Dubin and Johnson[2] and Sprinz and Nelson.[3] In the past four years an additional 36 cases have been reported, bringing the total to 50—from which it may be inferred that the condition is by no means as rare as was at first thought by its discoverers. A summary of these 50 cases by Dubin[4] should prove a valuable basis for further work.

Dubin suggests that the fundamental defect is a genetically determined impairment of the excretory functions of the liver, which reveals itself clinically in intermittent attacks of jaundice with biliuria and sometimes pale stools. The onset may be insidious or acute, resembling an attack of infective hepatitis, or may follow some other disease or stress such as pneumonia, pregnancy, or immunisation. The attacks are usually associated with malaise, pain in the right hypochondrium, nausea, and vomiting and diarrhœa. Between the attacks the jaundice almost disappears, although in most cases the serum-bilirubin remains more or less increased. Laboratory investigations indicate an obstructive type of jaundice, since some 60% of the serum-bilirubin is of the direct-reacting variety and bile is present in the urine, and, although the serum-alkaline-phosphatase is rarely increased, there is little evidence of parenchymal damage and the serum-proteins are within normal limits. It is, therefore, hardly surprising that in 31 of these 50 patients laparotomy was undertaken for the relief of biliary obstruction; this was not found in a single case, although gallstones were present in 5. Of these first 50 patients only 9 were women, but, since the American Armed Forces Institute of Pathology was the chief case-finding source, the sex-distribution is obviously biased. The world-wide distribution of sporadic cases suggests that all ethnic groups are susceptible.

The morbid anatomy of the condition has been studied almost exclusively by biopsy, either by needle aspiration or laparotomy. The one outstanding abnormality is the remarkable colour of the liver—variously described as black, green, or mahogany—owing to accumulation in the centrilobular cells of large amounts of coarse yellow-brown pigment granules. These give histochemical reactions that identify them most closely with the lipofuscins, from which they differ mainly by their coarseness and persistence. Other hepatic abnormalities such as necrosis or fatty infiltration are rare and may be regarded as mainly incidental. Repeated biopsies with intervals of up to four years have shown no evidence of progressive hepatic injury, and this is confirmed by the complete lack of correlation between the duration of the disease and the intensity of the hepatic abnormality, as well as by the excellent prognosis as regards life expectancy.

The nature of the underlying dysfunction is still not precisely known. Since the greater part of the serum-bilirubin is of the direct-reacting variety the fault cannot be in the mechanism that converts bilirubin to its glucuronide, but is presumably in the mechanism of excretion that follows this conjugation. Other evidence of impaired excretion is obtained with bromsulphalein, and from attempts to display the gallbladder by oral cholecystography which were successful only once in 37 patients The highly characteristic accumulation of pigment in the liver cells is presumably also the result of impaired excretion since the liver normally excretes lipofuscin pigment [5,6] The biochemical steps of these various excretions are still almost unknown, and it may reasonably be hoped that much will be learnt from further studies of these cases of chronic idiopathic jaundice

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[1] Lancet, 1954, ii, 1111.
[2] Dubin, I. N., Johnson, F. B. Medicine, 1954, 33, 155.
[3] Sprinz, H., Nelson, R. S. Ann. intern. Med. 1954, 41, 952.
[4] Dubin, I. N. Amer. J. Med. 1958, 24, 268.

PULMONARY ALVEOLAR PROTEINOSIS

KNOWLEDGE of pulmonary pathology has been greatly extended in recent years For instance, interstitial pneumonia due to infection with *Pneumocystis carinii* has been firmly established as an entity with characteristic histopathological changes, and progressive interstitial fibrosis of the lungs (Hamman-Rich disease) and alveolar microlithiasis have been thoroughly investigated Now a new pulmonary disorder has been described by three distinguished pathologists from the Harvard Medical School, Yale University, and the Armed Forces Institute of Pathology [7] Rosen et al name the disease "pulmonary alveolar proteinosis", and their conclusions are based on study of biopsy material from 27 patients 8 died, and in 7 of these necropsy material was available

There was only 1 child affected, almost all the patients were aged 20–50, and males were two and a half times as commonly affected as females The disease is chronic and its onset insidious, in some cases it is heralded by a short febrile illness, but in others there is no fever Progressive dyspnœa and a cough, which is usually productive, are the presenting symptoms Physical signs are few and, apart from neutrophil leucocytosis, which is common, laboratory findings have not proved informative X-ray examination shows at the height of the illness a "fine, diffuse, perihilar, radiating, feathery or vaguely nodular, soft density" with a "butterfly" distribution The disorder may be confused with sarcoidosis, though the hilar lymph-nodes are apparently not involved Rosen et al found on histological examination that the terminal air-spaces were filled with granular or homogeneous eosinophilic material which was strongly positive to periodic acid/Schiff (P A S) The P A S reaction was reversibly blocked by acetylation but was unaltered by saliva digestion The material stained pale blue with Hale's reduced iron method, and was metachromatic, and the metachromasia was increased by sulphation The presence of a polysaccharide was thus well established Lipids were demonstrable in frozen sections by Sudan and oil-red-O Cholesterol was present but phospholipids were apparently absent A protein component was revealed by a weak Millon reaction Rosen et al term the material "proteinaceous" and consider it to be the result of transformation of septal cells which increase in number and size In all cases laminated, strongly eosinophilic, and P A S -positive intra-alveolar bodies, 2–30 μ in diameter, were seen Some of these stained deep blue with phosphotungstic-acid hæmatoxylin, and none was calcified Rosen et al believe that, when septal cells disintegrate, they may form a nidus for deposition of proteinaceous material and thus the formation of the laminated bodies Cellular infiltration of interalveolar septa was absent or minimal The honeycombed masses which are so characteristic of pneumocystic pneumonia were not seen in pulmonary alveolar proteinosis The disorder is quite distinct from pneumocystic pneumonia and from microlithiasis alveolaris Extensive bacteriological, virological, and serological investigations failed to disclose an organism responsible for the disease On the other hand case-histories and histological findings suggest that the cause is inhalation of some irritant substance Neither antibiotics nor corticoids have proved conclusively beneficial Spontaneous improvement was not unusual, but, although some of the patients were observed for several years, in only 1 instance was clinical recovery associated with disappearance of radiographic signs

HISTAMINE HEADACHE

FOR almost a century a type of episodic headache has been recognised in which unilateral pain is accompanied by ipsilateral nasal congestion, conjunctival suffusion with lacrimation, and often erythema of the face It has usually been regarded as a variant of migraine In 1939 Horton et al [1] described it again and pointed out that it could often be precipitated by injection of histamine In subsequent papers Horton suggested that it was due to abnormal sensitivity to histamine and could be cured by graduated desensitisation

There is no doubt that such a discrete clinical entity exists within the group of episodic unilateral headaches The condition is commoner in men than in women, and more recent descriptions [2,3] have added to the syndrome a tendency for the headaches to occur in groups Thus they may come on several times a day, sometimes mainly at night, for a few weeks and may then be absent for weeks or months If histamine is administered during a bout of attacks it rarely fails to provoke one, but between times it may not do so Nevertheless the specific causal role which Horton assigned to histamine, and the benefits he claimed for histamine desensitisation, have not been widely confirmed Some cases are substantially improved for a long time, but many soon relapse, and in some repeated desensitisation has no effect Moreover antihistamines also usually prove valueless in treatment On the other hand ergotamine tartrate commonly aborts an attack, especially if given early, and Symonds [3] has claimed good results from administration of prophylactic intramuscular ergotamine at times when a series of attacks is known to be imminent, such prophylaxis is often practicable because in many cases the attacks have a fairly fixed time of onset in the twenty-four hours In a review of 20 cases Robinson [4] recommends ergotamine, if feasible prophylactically, as the best treatment—though he still prefers to differentiate the syndrome from migraine It is doubtful whether this distinction can be maintained The precise nature of migraine still escapes us, though its end-result as a localised vasomotor disorder is more clearly understood, but there is nothing which excludes the so-called histamine headache as a variant of migraine Indeed it would seem reasonable to regard it as one of those varieties which are triggered by allergens—a view supported by its seasonal incidence in some cases

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DR DANIEL THOMSON, a principal medical officer of the Ministry of Health, has been appointed a deputy chief medical officer in succession to Dr G A Clark, who retires on Sept 30

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[5] Hamperl, H *Schweiz Z allg Path* 1953 16, 399
[6] Bachmann K D *Virchows Arch* 1953, 323 133
[7] Rosen, S H , Castleman, B , Liebow, A A *New Engl J Med* 1958, 258, 1123

[1] Horton, B T , McLean, A R., Craig, W M *Proc Mayo Clin* 1939, 14, 257
[2] Ekbom K A *Acta psychiat Kbh* 1947, suppl 46
[3] Symonds, C P *Brain* 1956 79, 217
[4] Robinson, B W *Medicine*, 1958, 37, 161

Congresses

CANCER

THE Seventh International Cancer Congress (under the auspices of the International Union against Cancer) was held in London from July 6 to 12, under the presidency of Sir STANFORD CADE The first of these conferences was held in London thirty years ago At that time no pure carcinogens were known, no hormone had been isolated in the pure state, and no inbred strain of mouse was available in this country In the intervening years a vast amount of work has opened new ways of approach which are reflected in the membership of approximately 2500 persons and in the variety of subject treated in the 600 papers which were presented To those who knew the earlier conferences it is strange that so little time should be devoted in this one to descriptions of new carcinogens and to pathological anatomy The emphasis is much more upon mechanisms than upon causative agents, and there is a noteworthy attempt to relate experimental work to the disease in man Outside the laboratory the the epidemiological approach is increasingly to the fore

Epidemiological Studies in Cancer

As Dr PERCY STOCKS (Britain) said to the section on population studies, the epidemiology of malignant disease can be approached through three main avenues (1) the vital statistics of mortality from cancer of specific types in different sections of the population grouped according to the information given at the time of a national census, (2) morbidity-rates based on some system of notification and registration of cases, usually in the catchment area of cancer-treatment centres, and (3) special surveys, either retrospective or prospective, of particular subgroups in the population

All these methods were exemplified in reports to the congress, and their general intention was to relate the onset of malignant change to environmental circumstance or personal characteristics or habits such as age, sex, race, diet, and smoking Since, strictly speaking, we are concerned with the factors which favour the onset of cancerous disease, Dr Stocks believes that attention should be concentrated on "inception"-rates based on the date of the onset of symptoms and signs of the cancer rather than on the conventional "incidence"-rates based on the year and age of either registration or death He has used this approach in his own studies in a five-year survey of the Liverpool hospital region and North Wales—an area with a population of some 2$^1/_2$ million

Inception-rates were derived from death registration, where the certification of cause of death was checked by comparison with hospital and necropsy records, as well as from admissions to hospital These inception-rates could thus be related to the various characteristics of the population in the area classified either in the usual way by age, sex, occupation, and housing, or according to the results of interviews with the patients themselves and a group of "controls" matched by age Where the patient had died, health visitors elicited from relatives histories which, when checked against the responses given by some of these patients while in hospital, proved surprisingly accurate At the same time, collaboration with the Medical Research Council and the Fuel Research Station allowed estimates to be made of the concentration of certain polycyclic hydrocarbons, trace elements, sulphur dioxide, and total smoke in the air at different points in the region In the same way, samples of the soil in the gardens of patients who had died from cancer and corresponding controls were analysed for certain chemical characters and trace elements[1] Cancer of the lung, although exhibiting the usual relationship to smoking, also appeared to be associated with local air pollution levels

Dr P F DENOIX (France) observed how vital-statistical rates could be used to compare the varying trends in mortality from cancer of the breast and uterus in different countries in recent years In general, there seems to be a tendency for a concurrent increase in the death-rate from breast cancer and a decrease in the rate for cancer of the uterus

Dr E PEDERSEN, of the Norwegian Cancer Registry, illustrated the value, actual and potential, of the efficient system of cancer registration which has been built up in his country since 1952 The records give a strong hint that such schemes, designed to stimulate interest in cancer detection, can bring cases to notice earlier, but the diagnostic cross-checks also give a useful warning against a too literal interpretation of apparent urban/rural differences in cancer mortality On the other hand, the registration system has revealed geographical trends in mortality, such as a gradual increase in cancer of the thyroid from south to north, which are unlikely to be explained by regional differences in diagnostic facilities and skills

Dr Pedersen also described how in Norway advantage has been taken of the work of the Norwegian Cancer Society to elicit, by specific questions, data on menstrual and reproductive histories for a large number of presumably healthy women, whose subsequent experience of breast cancer will be determined by an intensive follow-up through the cancer registration system during the next few years

In much less sophisticated conditions, Dr J HIGGINSON (South Africa) has conducted surveys of cancer incidence among the indigenous communities of Africa Here, sample inquiries combined with sociological studies have been needed to fill in the picture which would have been obtained by routine census data in more highly developed countries Much emphasis was placed on the results of necropsy, and Dr Higginson affirmed that cancer of the liver, œsophagus, and sinuses and Kaposi's hæmangiosarcoma are commoner in Bantu males than in United States Whites The Bantu female suffers excessively from cancer of the cervix Cancer of stomach and large bowel are rare in both sexes

Cancer of the Lung

In the United States, Dr H F DORN has conducted a survey of mortality by cause among 290,000 men who in December, 1953, were holding United States Government life-assurance policies Most of them had served in the first world war, and a detailed history of smoking habits was obtained from 83% of them For both respondents and non-respondents, information on the cause of death was collected from death certificates and by special inquiry from the attending physicians The results were expressed in terms of the ratio of the deaths actually observed among smokers of various kinds to the numbers expected at the age-specific death-rates among the non-smoking section of this particular insured group Thus in total mortality this ratio ranged up to 1 58 for those who had smoked only cigarettes—i e , they had a death-rate 58% greater than non-smokers of the same age Regular cigar or pipe smokers, on the other hand, had a ratio of practically 1 That it is rarely too late to change is suggested by the fact that those who had given up regular cigarette smoking had a rate only 31% higher than that of non-smokers As might have been expected from other studies, the highest ratio was for cancer of the lung, among regular cigarette smokers the rate was nearly ten times that for non-smokers These regular smokers also suffered an increased risk of dying from diseases such as bronchitis, pleurisy, and emphysema, peptic ulcer, and cirrhosis of the liver, while their death-rate from coronary-artery disease was 63% higher than the rate for non-smokers Some of these associations, such as cirrhosis and some forms of cardiovascular disorder, may result from the excessive consumption of alcohol to which some heavy smokers are prone, but the close correlation of lung cancer with cigarette smoking cannot be lightly dismissed

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[1] Stocks, P Annual Report of the British Empire Cancer Campaign, 1957, supplement to part II London, 1958

This latest and striking confirmation of a long series of retrospective and prospective inquiries incriminating cigarette smoking as an ætiological factor in cancer of the lung gave fresh impetus to the discussion of that subject in other sections of the congress

Dr **Richard Doll** reviewed some of the accumulated evidence and discussed its interpretation Berkson[2] has suggested that the association between cigarette smoking and cancer of the lung may be an artefact produced by some peculiarity of the method of investigation Both cigarette smoking and the certification of cause of death are subject to error, and the group observed is inevitably a biased sample of the whole population Again, the association is not confined to cancer of the lung These facts, Berkson asserts, may invalidate the conclusions to which they seem to lead To this Dr Doll retorted that, although not unique, the association of cigarette smoking with death is far closer for lung cancer than for any other cause, and that the quantitative relationship between cigarette consumption and lung-cancer death risk is remarkably constant in many studies

That incipient cancer would stimulate the desire to smoke was unlikely, Dr Doll thought, for smoking often begins forty years before any symptoms and signs of the disease become manifest Nor does there seem to be any good reason to believe that such a close association is due to some third agent which is common to both cigarette smoking and the risk of lung cancer Hereditary tendencies and air pollution may be relevant factors, but their presence is insufficient to explain the increasing incidence of the disease in cigarette smokers of the present generation Experience with industrial and other forms of exposure to lung irritants suggests that cigarette smoking has a similar effect, in that it increases the risk of lung cancer without decreasing the risk of cancer of other sites

The weakest points in the cigarette theory of lung-cancer causation are the similarity in the experience of those who describe themselves as inhalers and those who deny inhaling, and the disparities between the lung-cancer death-rates in countries with similar cigarette consumption There may be physical explanations for the surprisingly favourable experience of inhalers The irregularity of the national rates may derive from differences—e g , in the amount of the cigarette actually smoked—which are now being investigated in several countries

Against these imperfections in the crude epidemiological data must be put the striking contribution to geographic pathology described by Prof **Leiv Kreyberg** in a congress lecture He pointed out that primary epithelial lung tumours do not constitute oncological entities although, in both mortality and morbidity statistics, they are treated as such Inevitably this leads to an obscuring of the pattern of epidemic behaviour which can be clarified only by more detailed study of the histological character of the tumours themselves A careful review of some 1000 cases suggested that lung cancers could be divided into two groups on the basis of reasonably objective criteria Group-I tumours included squamous-cell, large-cell, and oat-cell carcinoma, group II comprised adenocarcinoma, bronchiolar-cell carcinoma, benign and malignant adenoma, and salivary-gland tumours The importance of this distinction lies in the demonstration that group-I tumours, which increase in frequency with age, are related to exposure to irritants of all kinds including cigarette smoke, whereas the group-II tumours may occur even in young adults and with equal frequency in males and females, in different occupations and in town and country Because of the constancy in the incidence of this second group of tumours, the ratio of group-I to group-II tumours in any unselected series of lung neoplasm may be very useful in epidemiological studies As Professor Kreyberg showed, the ratio goes in step with the increasing incidence of lung cancer associated with cigarette consumption and may thus act as an index of changing circumstances in the natural history of the disease He also showed that this classification could be made quite objectively without reference to the patient's smoking or other history, and if standardisation of his procedures on an international scale can be achieved, there will be a bright prospect for epidemiological studies based on comparisons of such ratios even in countries without effective registration systems

When similar pathological distinctions were looked for in the lungs of guineapigs and rats which had been injected intrapleurally with chromite ore roast, Dr **W C Hueper** (U S A) reported, squamous-cell carcinoma, adenocarcinoma, and other malignant and premalignant types of change were found The carcinogenic properties of metals and minerals such as chromium, nickel iron oxide, radioactive metals, arsenic, and asbestos have been most strongly suggested, however, by the epidemiological evidence of excessive mortality from lung cancer among men exposed to such dusts by their work

These studies of lung-cancer mortality after occupational exposure to dusts again raised the question of air pollution in our industrial cities as a possible cause of the rising incidence in this country, and Mr **R E Waller** (Britain) reviewed the evidence for such an effect He pointed to Stocks' finding of higher lung-cancer death-rate in large towns than in rural districts, but then went on to suggest that the mortality experience of successive cohorts of men in town and country was quite consistent with the gradual spread, during this century, of the habit of cigarette smoking outwards from the main population centres

The mounting evidence against cigarette smoking has inevitably turned attention to the possibility of reducing the associated risk of lung cancer Dr **E L Wynder** (U S A) described a series of experiments designed to identify the carcinogenic elements in cigarette smoke and the critical features of their production which might be modified to reduce their noxious action Better filtration of tobaccos chosen for their low tar content is one alternative, removal of the precursors of the carcinogens produced by pyrolysis is another He illustrated some hopeful studies on the results of variation in burning process which hold out the prospect of a worth-while modification of the burning qualities of cigarettes As long as cigarette smoke remains for most people an incurable addiction, such modifications are the only hope of mitigating the current epidemic of lung cancer

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[2] Berkson, J , *J Amer stat Ass* , 1958, 53, 28

Mammary Cancer

Dr Charles Huggins (U S A) reviewed the hormonal ætiology and treatment of breast tumours in masterly fashion

In a symposium on the clinical management of breast cancer, the consensus of opinion was that radiotherapy judiciously applied offers the greatest chance of improving the results of mastectomy, but in the view of Mr Hedley Atkins (Britain) the extreme radiotherapeutic techniques advocated by McWhirter still needed substantiation by a controlled trial

Dr C D Haagensen (U S A) stressed the importance of selecting treatment to suit the stage of the condition He described his technique of triple biopsy of the primary tumour, the internal mammary glands, and apical axillary glands, on the results of which the decision as to treatment is largely based In early cases thus selected he recommended radical mastectomy

Prof D W Smithers (Britain) reviewed the factors other than treatment which affect the prognosis, laying particular stress on the histological type of the tumour and emphasising the great difficulty in excluding biological factors when attempting to evaluate treatment

Mr R S Handley (Britain) summarised his observations on the importance of spread to the internal mammary glands, especially in tumours affecting the inner half of the breast. In his series of 150 patients submitted to radical mastectomy with intercostal biopsy, who were followed for five years or more, of those with no glandular involvement 84% were alive and well, whereas of the 41 patients with involvement of both sets of nodes only 2 were alive

Dr M. Margottini (Italy) summarised the arguments in favour of extended radical surgery in the treatment of carcinoma of the breast He emphasised that this operation does not increase the number of operable cases, but, in contrast to some other speakers, he thought it might improve results, though it is too early yet to reach conclusions

Dr F Baclesse (France) reported his results in the treatment of carcinoma of the breast by radiotherapy alone Prof S A Kholdin (U S S R) discussed the management of the disease in general, laying particular emphasis on the need to modify treatment according to the extent of spread

Dr A Loufty Aboul-Nasr (Egypt) discussed the treatment of patients with advanced, widespread disease He recommended oophorectomy particularly in such cases occurring before the menopause, reporting that in his experience this produced a remission in 40% He felt that generally hormone therapy gave better results than chemotherapy

Dr R Luft (Sweden) also recommended oophorectomy for women with advanced carcinoma who were still menstruating or were only one year postmenopausal In his experience, if this produced no remission, then no benefit was likely to follow adrenalectomy In postmenopausal cases it is his practice to prescribe œstrogens, and if this produces a remission the patient is likely to benefit from ablation of the pituitary or adrenals He suggested that hypophysectomy generally produced a longer and more complete remission

It was apparent that adrenalectomy is a much more feasible routine treatment than hypophysectomy, owing to the greater and rarer skill required for the latter operation But implantation of radioactive yttrium into the hypophysis (described by Mr A P M Forrest [Britain]), causing more or less total destruction, may in future be practised at many centres if a more reproducible technique proves effective

As regards the important decision whether abortion is justified in mammary cancer occurring during pregnancy, the general opinion was that this was desirable only during the first trimester, and that the hormonal conditions during the latter stages often antagonised the disease

At this panel meeting a wide range of questions was submitted by the audience The different opinions expressed by the experts emphasised in a dramatic and stimulating way that advanced thought on this subject is now passing through a shifting, formative phase

In experimental mammary carcinogenesis Dr Huggins and Dr Harry Shay (U S A) showed the value of intensive limited carcinogen treatment of rats to produce either dependent mammary neoplasms or latent carcinomas on which hormonal influences could be investigated

Cancer Detection by Cytological Methods

Dr Ruth Graham (U S A) and Prof H C McLaren (Britain) described methods of screening patients for carcinoma of the cervix in a cancer hospital and a general gynæcological clinic respectively The number of patients investigated is impressive—amounting to many thousands—and Professor McLaren was clear that this method is of little value in the detection of invasive cervical cancer (where clinical methods of diagnosis are adequate) but would pick up 4–5 cases per 1000 of "carcinoma in situ" The problem is then how to treat these patients, who should be able to expect a cure Half may be cured by ring biopsy, but the remainder will eventually need hysterectomy and all must be kept under constant cytological investigation

Dr L V Ackerman (U S A) discussed cytological examination of the spectrum after aerosol stimulation of the air passages, and suggested that all men over 40 years of age who are heavy smokers and live in a polluted atmosphere should be screened in this way

Prof J B Duguid (Britain) described his personal change of opinion in regard to the cytological examination of gastric washings for diagnosis of early stomach cancer and emphasised some very important points This is not the kind of work for a small hospital laboratory—it is the work of a specialist The surgeon and the pathologist should be aware of the difficulties, and of the need for an adequate specimen, representing all parts of the stomach mucosa and reaching the laboratory quickly Malignant cells will rarely be present in large numbers, repeated examinations may be necessary, and it will not always be possible to say whether the cells seen are malignant or not

Running through these papers was the knowledge that these examinations are costly and time-consuming It is computed that to screen 6000 persons for cervical carcinoma, 1000 hours at the microscope are required Suggestions for selection of patients for screening tests included omission of those under 30, those who have not borne children, and practising Jewish women, in whom cancer of the cervix is rare A point of controversy concerned the responsibility for the diagnosis Professor McLaren thought that the technicians who do the screening should accept responsibility for diagnosis, while Professor Duguid thought that only a pathologist with a good knowledge of morbid histology should undertake this It seemed clear that the help of technicians is essential for large-scale screening

Ætiology of Cancer of the Bladder

Dr Georgiana Bonser (Britain) described the work leading to the conclusion that 2-naphthylamine was carcinogenic to the bladder of man and the dog by virtue of its conversion to 2-amino-1-naphthol Metabolic studies had revealed the importance of this transformation, and the findings had been confirmed by the technique of bladder implantation

Dr Bonser discussed the extension of this work to the other industrial aromatic amines and hypothetically to other chemical compounds The orthohydroxyamines were of importance in amine carcinogenesis in general

Prof E Boyland (Britain) described two possible ways in which the carcinogenic compounds might be liberated—namely, by the action of glucosiduronidase on glucosiduronidate, and by phosphatase on phosphate—and he discussed the possible action of enzymes on metabolites which have yet to be discovered

Dr W F Melick (U S A) described the incidence of industrial bladder tumours in workmen exposed to *p*-xenylamine Since his original communication further tumours have been found The degree of exposure of workmen was severe, judging from the amount of free xenylamine found in their urine, and the shortest exposure leading to the formation of a tumour was only 131 days Dr Melick indicated that ureteric and pelvic tumours had occurred in his series

Dr J L Billiard-Duchesne (France) surveyed the occurrence of benzidine bladder tumours in the workers in the French chemical industry He said that this was in line with the findings in other countries with an established chemical industry He strongly recommended the routine cystoscopy of workmen engaged in hazardous work, and that this be extended to all workpeople who had been in the industry for fifteen to twenty years

Dr J Clemmesen (Denmark) described a statistical investigation of papilloma of the bladder amongst an urban and rural population in Denmark His evidence suggested, although far from conclusively, that there was a connection with tobacco smoking

A number of papers dealt with related topics Prof R Truhaut (France), Dr D B Clayson (Britain), and Mr L Bradshaw (Britain) each described a particular aspect of the fate of an aromatic amine in the animal body These studies showed that orthohydroxyamine conjugates were formed from benzidine and 4-aminodiphenyl Mr Bradshaw showed that the urine of rodents dosed with 3-hydroxy-4-nitrodiphenyl contained more 3-hydroxy-4-aminodiphenyl than did the urine of rodents to which 4-aminodiphenyl had been administered

Dr H R Gutmann (U S A) demonstrated in the case of an orthohydroxyamine derived from 2-acetylaminofluorene that protein binding was possible in simple biochemical systems

Dr R R Brown and Dr J M Price (U S A) showed that patients suffering from cancer of the bladder often metabolised tryptophan to orthohydroxyamine derivatives more readily than normal persons This effect is reversed if vitamin B_6 is administered In view of the suggestive evidence of Boyland and his co-workers that 3-hydroxyanthranilic acid may be carcinogenic, this indicates a possible mechanism by which some spontaneous tumours may arise

Carcinogenesis

Dr I Berenblum (Israel) discussed the possible relation of metabolism of carcinogens to their action and suggested that with the polycyclic hydrocarbons the evidence did not permit of any conclusion as to whether the carcinogen or its metabolite was decisive in carcinogenesis He mentioned the possibility that hydroxylation followed by methylation preceded carcinogenesis, but again he said he could offer no evidence With the amines, however, there was evidence that 2-amino-1-naphthol was carcinogenic, whereas 2-naphthylamine was not Protein binding and the protein deletion hypothesis were too unspecific to lead to a satisfactory theory The metabolism of urethane suggested that changes in the nucleic acid induced by this chemical or its metabolites might be connected with carcinogenesis, but the evidence was not complete In conclusion Dr Berenblum thought that perhaps we were wrong in looking for a unifying theory of cancer, and that the disease might have multiple origins

The use of a new experimental species in cancer research was described by Dr H E Pogosianz (U S S R) and her collaborators, who have investigated the Steppe-lemming and found it to be similar to the mouse Mouse sarcoma 180 has been transplanted into this species without the use of adjuncts to depress immunogenic resistance This animal is resistant to ectromelia

Dr J G Fortner (U S A) has investigated the effects of implanting pellets into the gallbladder of cats Pellets containing the known carcinogen methyl cholanthrene induced tumours, whereas pellets containing bile extracts or gallstones were negative This worker also found a wide variety of spontaneous tumours in his colony of Syrian hamsters

The induction of cancer of the stomach in the experimental animal remains a difficult problem Dr S C Skoryna and his colleagues (Canada) have repeated the observation that it may be induced with carcinogen-impregnated threads, while Prof Olav Torgersen (Norway) is continuing an investigation into the effects of heated fat

The main difficulty with the electron distillation theory is that, however precise the electron density calculations, they must be correlated with imprecise biological data

Dr Ronald Mason (Britain) has used the molecular orbital theory to study the forces operating between the carcinogen and the protein with which it is interacting At present this idea does not seem to be capable of experimental test and its relation to practical carcinogenesis is obscure

The present state of the experimental investigation of protein binding of the hydrocarbons was described by Dr Charles Heidelberger (U S A), who believes that this is correlated with carcinogenic activity He was unable to suggest any evidence as to the nature of the essential enzymes which were "deleted" as a result of protein binding Dr D L Woodhouse (Britain) has been unable to obtain convincing evidence that protein binding is in any way specific—possibly because of experimental difficulties in the system he studied

Immunology and Immunogenetics

Dr E Weiler (U S A) showed that organ-specific antigens are lost from rat liver and hamster kidneys in the process of carcinogenesis By a series of ingenious isotopic techniques combined with standard immunological methods, he found that normal hamster kidney grown in vitro also loses these organ-specific proteins after a short time His work directly supports that of Prof H N Green (Britain) on the immunological deletion of organ-specific antigens in carcinogenesis But Sir Macfarlane Burnet (Australia) in an impartial survey of the biological aspects of cancer concluded that these stimulating ideas needed more critical experimental backing

Dr Ilse Lasnitzki (Britain) illustrated how organ culture techniques can be applied to fundamental biological problems, and emphasised the advantage of these methods over the in-vitro cultivation of single cell species

The evergreen topic of virus involvement in cancer ætiology attracted much discussion, but in comparison with previous times interest in this field of research seems to have diminished In particular no-one pursued the idea that human mammary cancer was of viral origin Sir Macfarlane Burnet concluded that viruses have no significant role in human cancer except for possibly some part in the induction of leukæmia

Hormones in Genesis of Cancer

Prof O Muhlbock (Holland) presented evidence substantiating the idea that hyperhormonal pituitary stimulation can lead to cancer of the target organ This aspect has been broadened by the Dutch workers' demonstration, described by Dr L M Boot, that breast carcinoma can be induced in milk-agent-free mice by the repeated subcutaneous implantation of pituitaries from animals of the same strain

Ovarian carcinogenesis was discussed by several workers, among whom Prof A Lipschutz (Chile) made a notable contribution He suggested that the origin of so-called granulosa cell tumours of the ovary might in some cases be in the ovarian stroma, and he described the histological changes occurring in the evolution of these tumours produced by intrasplenic grafting or subtotal castration Apparently the sequence of changes in the two methods is similar, but in the ovarian fragments in situ the malignant transformation does not usually proceed beyond the stage of luteoma during the lifetime of the animal

Induction of ovarian carcinogenesis by a newer method was described by Dr J Marchant (Britain), who showed that in the ovaries of mice, treated for a limited time with 9 10 dimethyl 1 2 benzanthracene, transplanted to the ovarian capsules of untreated animals, tumours still occur to the same extent and in much the same time Normal ovaries, however, do not develop into tumours when transplanted into mice which have previously been treated with the carcinogen

Dr F Bielschowsky (New Zealand) described the evolution of autonomous growth in thyroid neoplasms and correlated this with their dependence on secretion of thyroid-stimulating hormone (T S H) by the intact pituitary

Dr S H Wollman (U S A) showed that the ability of individual thyroid tumours to take up iodine could be a measure of their malignancy—although in some instances, paradoxically, the hypersecretion of the tumour completely inhibits T S H production, illustrating the autonomous nature of the particular growth

Dr J Furth (U S A) described the multiple potentialities of tumour production in the irradiated pituitary and showed how functional neoplasms of different types could be obtained This approach to carcinogenesis obviously holds out hope of considerable advances in knowledge of the normal interrelations of the endocrine system

Chemotherapy of Cancer

Dr C C Stock (U S A) reviewed the problems in setting up an efficient screening programme for thousands of compounds The ideal of testing every compound against every test system being impracticable, the quick type of microbiological investigation is probably the best preliminary test, followed, in the case of promising materials, by more thorough testing against a range of animal tumours and human tumour implants This secondary investigation should include tests against a solid tumour, an ascites tumour, and a leukæmia, with human tumours carried by implantation as preferable additional systems It was generally thought best to err on the side of using test tumours very sensitive to drug action, leaving tests on the spontaneous, and usually more resistant, tumours to later stages of the programme

Prof T Yoshida (Japan) emphasised that laboratory tumours rarely metastasised, so that this important facet of neoplasia in man is in danger of being insufficiently attacked His group have therefore produced strains of ascites tumours, especially hepatomas, where invasion of the blood-stream by tumour cells can be seen as early as twenty-four hours after implantation

Prof A Haddow (Britain) suggested that prevention by chemotherapy might be easier to attain than outright cure, and he described a series of compounds which, in the laboratory, would totally inhibit the growth of implants of Walker rat carcinoma Another series of compounds related to the alkylating agents (in the development of which the Chester Beatty Institute have played a large part) were much less toxic to the host than those presently used But however bright this experimental picture appears, Dr Haddow's healthy scepticism led him to predict that the future of chemotherapy lay in fundamental studies of the normal and neoplastic cell rather than extension of cytotoxic or cytostatic principles

Dr G Mathé (France) discussed the treatment of neoplasms of the hæmatopoietic system with substituted di-ethylene-imine-benzoquinones, and the subsequent discussion ranged from the problems of drug resistance to the question whether in health man has inherent defence mechanisms against malignancy

Dr S Farber (U S A) gave a comprehensive review of chemotherapeutic agents whose mode of action is that of an antimetabolite, an antibiotic, or an anti-enzyme, with particular emphasis on actinomycins C and D and the anti-folic-acid drugs After emphasising that tumour retrogression by chemotherapy alone, while uncommon, was not unknown, he suggested that the day would come when every malignant condition would respond to therapy by compounds completely non-toxic to the host, and that even active immunisation against all types of cancer would finally be achieved

Prof L F **Larionov** (U S S R) described the experience of some Russian clinics with various types of alkylating agents, and indicated that better effects were to be expected by combining the active alkylating centre through a natural aminoacid to another carrier such as a vitamin or peptide, so lessening host reactions Of great interest was his evidence that certain types of malignancy, notably Hodgkin's disease, could be cured by alkylating agents alone provided that the dosage was properly controlled, pushed to the limit of the patient's tolerance, and continued by maintenance and, finally, prophylactic therapy

CHEST DISEASES

The triennial discussions on tuberculosis in the Commonwealth countries, which the National Association for the Prevention of Tuberculosis has fostered in the past fifteen years, have been steadily broadened both clinically and geographically This year's conference, held in London on July 1–4, was combined with the annual conference of the British Tuberculosis Association and was attended by delegates from countries and dependencies in all five continents

Anti-tuberculosis Campaign

Dr **Johannes Holm**, chief of the Tuberculosis Section of the World Health Organisation, epitomised his outlook in the declaration "Tuberculosis is a public-health problem as long as there is a risk of any individual in the community contracting the disease" Prevalence of *demonstrably infectious pulmonary tuberculosis* varies from a rate of 20 cases per 1000 adults in parts of Africa to 1 per 1000 in Denmark More than half the children aged 15 years in the Somalilands, Ethiopia, and West Pakistan show evidence of infection Indian surveys have surprisingly shown that tuberculosis there is as prevalent in village communities as in those of urban areas Mass vaccination with B C G, because it is effective and easy to arrange, is at present more widely applied in the world than is diagnosis and chemotherapy, whose practical application among scattered poor communities presents immense difficulties

In contrast to current trends in this country, several speakers made a plea for more hospital beds for tuberculosis, and more trained specialist staff, for tropical countries The dangers of giving isoniazid alone, and the paramount importance of effective chemotherapy were emphasised Relapses after even long-continued drug treatment was discontinued, and the emergence of resistant bacilli after too little chemotherapy, showed that tuberculosis treatment should still be a specialised enterprise

Infection in Laboratories

A series of papers described the hazard of tuberculous infection among laboratory workers from sputum containers, culture bottles, and laboratory animals The recommended prophylactic measures included air hygiene, personal hygiene, technique cleanliness, work supervision, and health supervision especially of junior staff, along with tuberculin tests and B C G vaccination on entry to the service and periodic chest X-ray examination Although this subject has produced a growing literature only in the past few years, it was in fact mentioned by Robert Willan [1] in his report on the diseases of London for the year 1800, in which he listed "bricklayers' labourers, laboratory men, coalheavers and chimney sweepers" as specially liable to "obstinate pulmonic diseases terminating in consumption".

Surgery for Pulmonary Tuberculosis

The place of surgery in treating pulmonary tuberculosis was debated with great vigour round the lessons to be drawn from the report,[2] which we have lately reviewed,[3] of a widespread study of the results of thoracic surgery in the United Kingdom during 1953–54

It was made clear that a historical study of this kind has only very limited application to current circumstances The therapeutic compass today is pointing away from surgery in tuberculosis In 1957–58 in England and Wales 1168 collapse operations and 3380 resections were performed, compared with 4207 collapses and 3923 resections in a similar period four years ago Nevertheless it was significant to hear a senior hospital physician declare "I am not convinced now that chemotherapy is so dependable that consideration of surgical intervention is *no longer important*" Results after tuberculous lung surgery depend on the extent, destructiveness, and drug resistance of the disease, and the age and sex of the patient Adequate chemotherapy, says the report, is the most important factor in surgical success Women under 40 with limited unilateral lesions which were drug-sensitive showed the best results Yet these very criteria cannot fail to prompt the query, "Was your operation really necessary?" In surgery of all kinds, the best technical results are achieved in cases where operative interference is least necessary While the physician is compelled to turn to the surgeon for help with the patient whose cavity persists, excreting resistant bacilli, the surgeon will not welcome a patient on whom he must operate without benefit of effective chemotherapeutic cover It appears that in such cases modern thoracoplasty gives better results than resection in this country United States practice is different There collapse operations are being abandoned in favour of excisional surgery, but according to Dr J **Maxwell Chamberlain** (Columbia University) it is American practice to operate most readily on early cases, before chemotherapy has been long established—partly, it appears, because hospital stay is thereby shortened, and because there are pension-computing advantages to ex-Service patients who can show thoracotomy scars

Radiography

Mass radiography of the "hazard groups" in the community was confirmed as of value in eliminating sources of infection Household contacts, middle-aged and older men, lodging-house residents, tuberculin-positive adolescents, and unvaccinated immigrants who have been exposed to high infection risks here give the highest yield *There are still many adults in this country who have never been X-rayed*

On possible risks from diagnostic radiography it was reassuring to hear from Dr J F **Loutit** that the chance of serious genetic damage was negligible when well-maintained modern apparatus is used, with strict attention to technique designed to avoid radiation to organs containing *germinal* epithelium Frequently repeated exposure to diagnostic radiology *might* produce a summation risk of leukæmia, but even this danger was considerably reduced when only part of the body's bone-marrow was exposed to radiation On the whole it seemed that any very small risk there might be of leukæmia following diagnostic X-ray examination is enormously outweighed by the chances of early X-ray diagnosis of lung disease

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[1] Willan R Miscellaneous Works (edited by Ashby Smith), p 389 London, 1821

[2] Francis, R S, Curwen, M P Major Surgery for Pulmonary Tuberculosis London, 1958

[3] *Lancet* 1958, i, 1373

Atmospheric Pollution

Three centuries and more have passed since our King James I's[4] tirade and John Evelyn's[5] lament tried to influence public opinion against the pathological effects of "that hellish and dismall cloud of sea coale so universally mixed with the otherwise wholsome and excellent aer, that her inhabitants breathe nothing but an impure and thick mist corrupting the lungs so that catharrs, phthisicks, coughs and consumptions rage more in this one city than in the whole earth besides"

Much the same sort of complaint was made by Dr P J **Lawther** and others at the conference, when more evidence—chemical, physical, meteorological, and statistical—was adduced to correlate chronic bronchitis and lung cancer with particulate and gaseous pollution of the ambient air and with tobacco pollution of the bronchial mucosa Lawther defines three grades of atmospheric pollution

(1) An "acute" form, occurring when smoke is trapped under an immobile cold anticyclone air layer, also labelled "smog" This is an uncommon, freak, climatic event, fraught with fatal danger to old people and cardiorespiratory cripples

(2) "Subacute pollution," comprising the more frequent episodes of winter fog of short duration which spell exacerbation and relapse for the chronic bronchitic

(3) "Chronic pollution," Lawther's term for the endemic winter air contamination of English industrial towns The active principles of this pollution are mainly suspended carbon of various types, tars, and sulphuric-acid particles These are suspected to be the factors inducing recurrent bronchitis and lung cancer

This simple classification receives support in the analysis by Gore and Shaddick[6] of increased mortality in London during periods of measured varying atmospheric pollution, and in the second[7] of Reid's Milroy lectures

Cigarette Smoking

Prof **Alexander Kennedy** explained convincingly that only a sudden, determined, and complete wrench—if necessary by hypnosis—could enable the heavy cigarette smoker to give up his addiction Attempts at gradual reduction by self-rationing are less likely to succeed Supporting sympathy and restraint by relatives and friends are necessary

Tuberculosis and Sarcoidosis

One of the most exciting discussions dealt with the relationship between tuberculosis and sarcoidosis Dr J G **Scadding** cautiously defined sarcoidosis only in terms of its characteristic morbid histology—epithelioid-cell nodules without necrosis or round-cell infiltration and, in chronic lesions, with hyaline deposits Sarcoidosis could be a phase of tuberculous disease with weak tuberculin allergy Typical sarcoidosis has been identified in a patient who a few years earlier had tuberculous cervical glands from which human-type bacilli had been recovered Most cases of sarcoidosis show no response to ordinary antituberculous chemotherapy unless corticosterone is added In some, frank tuberculosis appears later, and with it is acquired tuberculin sensitivity with subsidence of the sarcoid lesions During cortisone therapy in sarcoidosis, it is common to witness the emergence of tuberculin sensitivity Though no bacilli have been demonstrated in sarcoid lesions, mycolic-acid residues characteristic of tubercle-bacillus breakdown products have been identified On ætiology Dr Scadding felt compelled to ascribe the majority of cases he has seen in this country to tuberculosis, but he would not exclude other possible causes such as beryllium, and in other countries there may be yet other excitants

It is interesting to compare this conclusion with one expressed twenty-eight years ago by Sir Archibald Gray,[8] who, in discussing subcutaneous sarcoid, is reported as saying he considered that these lesions represented a group of reactions rather than a specific disease and that some of the lesions might be tuberculous Interesting in this connection, too, are the lung nodules in Caplan's syndrome—the sharply defined round lesions found in the lungs of rheumatic coalminers, where no evidence of active tuberculosis and no bacilli are found, yet characteristic concentric tidal deposits of macrophages and coal-dust are seen among dense fibrous strands Here, too, mycolic-acid residues are demonstrable

An alternative ætiology for sarcoidosis was postulated by Dr **Harold L Israel** (Pennsylvania), who defined the condition as "a prototype of granulomatous reaction" increasingly prevalent in the United States, and rarely associated with erythema nodosum It is more than ten times as common in Negroes (especially young women) as in Whites The view formerly held in America that sarcoidosis is an atypical tuberculosis has now apparently been abandoned in favour of a notion that it is a specific allergic hypersensitivity reaction to an "inert" substance—possibly pine-tree pollen In supporting this hypothesis Dr Israel averred that most American patients with sarcoidosis came from pine-forest areas, and that pine pollen contains lipid and has acid-fast staining properties, and when injected into animals produces granulomas—though not in the lungs

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At the annual dinner of the British Tuberculosis Association on July 3, Dr **Owen Clarke**, the hon secretary, said that, whereas formerly the word "tuberculosis" carried a stigma for the patient, today it carries a stigma for the doctor Many chest physicians are almost ashamed that they handle cases of pulmonary tuberculosis, and seek to emphasise the wide range of other diseases in which they are masters What a tragedy of perverted thinking! For the duty of a good doctor is to restore his patient to full economic independence and social stability, and there is no branch of medicine in this country which teaches this principle so well as does tuberculosis work The chest physician is at the head of a team which is closely concerned with the treatment of disease, the social complications which may arise from it, and the public-health problems involved Does any other consultant really concern himself personally with all these aspects of medicine? On the clinical side, the Association's members have time to expand their work into other branches of chest disease, and their special training and experience makes them well fitted to do so But let them beware lest in trying to increase their importance they succeed only in diluting their special ability and lose their real understanding of good medicine Our own specialty, said Dr Clarke, is surely one of the most fascinating and progressive in medicine, and should continue to demonstrate that the treatment of sick people demands more than an interpretation of scientific jargon and even today is a human art involving the whole structure of the man's securities

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[4] A counterblaste to Tobacco London, 1604

[5] Evelyn J Fumifugium London, 1661

[6] Gore, A T, Shaddick, C W *Brit J prev soc Med* 1958, 12, 104

[7] Reid, D D *Lancet*, 1958, i, 1289

[8] Gray, A M H *Proc R Soc Med* August, 1930, p 1487

British Medical Association

ANNUAL REPRESENTATIVE MEETING

THIS year's Annual Representative Meeting of the British Medical Association, which ended at Birmingham on Monday, was not one of the liveliest of recent years. The announcement of the rejection of the claim for a further interim increase in remuneration was received with apparent inertia by an audience whose reactions seemed to have been deadened by past experiences.

The Association met under the presidency of Prof. A. P. THOMSON (Birmingham), and the Annual Representative Meeting was held in the great hall of the university at Edgbaston, with Dr. A. BEAUCHAMP (Birmingham) in the chair.

The Duke of Edinburgh had graciously consented to accept nomination for President, and the Association "honoured itself by electing His Royal Highness as President for 1959–60", standing orders being altered for the purpose.

NO INTERIM AWARD

Dr. SOLOMON WAND, chairman of council, told representatives that the Minister of Health had refused a further interim adjustment which had been requested because the Royal Commission on Doctors' and Dentists' Remuneration had not reported by Easter, as had been hoped. An application was made because of the previous Minister of Health's undertaking when the Commission was set up. Dr. Wand and others met Mr. Walker-Smith on June 17. "This letter was placed in my hand yesterday afternoon at 3 o'clock," commented Dr. Wand, holding up the Minister's reply on July 10. The letter recalled that when the medical profession's delegation came to the Ministry there was a $2^3/_4$-hour discussion. The Minister then gave, in what he described as "a highly summarised form", the reasons why he was not able to agree to an immediate further adjustment.

"You pointed out that my predecessor had undertaken that a claim could be considered if the Royal Commission had not reported by Easter 1958. (You will, of course, remember that my predecessor's letter of June 6, 1957, in which he gave this undertaking, concluded with the phrase 'But you will, I know, understand that it is impossible for me to commit myself in any way at this stage, when neither we nor you can have any idea what might happen in the interim or what such a claim might amount to.')

"The reasons why I am unable to agree that the circumstances warrant a further interim increase at the present time are broadly two-fold. In the first place, although the Royal Commission are not yet ready to report, they are pressing ahead with all speed and, assuming that their report is not unduly delayed, a further increase would run the risk of prejudicing their work. Secondly, the economic situation of the country at the present time must be taken into account. Circumstances since April and May, 1957, to date have not changed so greatly as to justify an increase. Moreover, no other people remunerated from the public purse who received a pay increase of 5% in April and May, 1957, have yet received any further award. A further award to the doctors might well lead to claims for increases in remuneration of an inflationary nature from others and it remains just as important as ever to secure stability in wages and salaries.

"It is of course open to the Association to make further representations at any time but what I have said in this letter represents the view I am bound to take at present."

Dr. Wand remarked that it had taken a long time since June 17 to say 'No'. Would an increase prejudice the Royal Commission? A new grade of registrar had been determined unilaterally by the Minister: did that prejudice the Royal Commission any less than an interim adjustment? How did the Minister know that the Royal Commission would be prejudiced by such a change? Dr. Wand had offered to write to the chairman of the Royal Commission to find out whether such an adjustment would prejudice the Commission.

Of the economic situation Dr. Wand declared: "Whenever we go the economic situation is wrong." But in any event what was the relevance of the economic situation? Had any other section of the community received only 5% increase since 1951? As to the Minister's statement that he would be pleased to receive further representations, Dr. Wand said: "We have heard that one before, but we are going back after all." He suggested that the representative body should have time to ponder on this letter and that discussion be deferred until later in the meeting.

After ten years of the National Health Service, Dr. Wand thought that the most important feature was the wonderful service that was being given to the public. The public had had wonderful value for its money. That was due to the devotion, in spite of many frustrations and disappointments, of those engaged in the practice of medicine and associated professions and callings. After ten years doctors could also say that their relationship with Government officers had been good, consistently good. When it came to the realms of higher policy, could the same be said about relations with the Government? (Cries of "no".) Dr. Wand said that he was not only thinking of remuneration when he said that the profession must be alive to the danger of unilateral decision. The unilateral decision, carried on indefinitely, would lead to control.

REVIEWING THE MEDICAL SERVICES

The representative body authorised the council, in consultation with the Royal Colleges, the Scottish Royal Medical Corporations, the College of General Practitioners, and the Society of Medical Officers of Health, to determine the size and the precise composition and terms of reference of the committee to review the medical services, and to appoint the chairman of the committee.

Dr. J. S. ROSS (East Herts) thought that doctors could not have the type of health service they wanted until it was known what form of service the majority of them would support. His motion to this effect was referred to council.

Dr. B. BURNS (Sheffield) was for saying what was known to be true, even if it was unpopular. This revelation turned out to be that the frustration of family doctors arose from two basic causes—the terms of service inseparable from capitation-fee remuneration, and the abuse of the "free" service by certain patients. A relentless minority of patients were cadgers and whiners who trifled with doctors' time and leisure. If patients wanted doctors' time, they must be prepared to have a value placed upon it. They must be prepared to pay for it. The capitation fee brought out the worst in the doctor, and the "free" system brought out the worst in the patient. But Dr. J. S. NOBLE (Morpeth) felt ashamed that the representative body was being asked to blame patients. "Doctors are responsible for running their practices," he said. "Responsible doctors produce respect."

A younger practitioner's view was put by Dr W P Lambie (Sheffield) The great majority of young practitioners, often insidiously prompted by those in high office to whom they looked for help and guidance, were clamouring for a full-time salaried service "We cannot continue as at present and the only real alternative to the capitation-fee remuneration is a fee per item of service" It would wipe out the present frustration and discontents, particularly if patients paid a proportion of the cost of the items at the time

PARKING PROBLEMS

"It is not impossible that if some solution is not found for doctors' parking problems, people living in the centre of big cities may not be able to obtain a National Health Service practitioner to look after them" Dr Wand's warning was referred to by Dr I M Jones, chairman of the private practice committee, who said it was quite impossible for a doctor to deal properly with a patient if he was all the time wondering whether his car would be there when he came out or whether he would be apprehended The Ministry of Health had offered to join a deputation to the Ministry of Transport Though the Minister of Transport at first refused to see the Association at all, he later agreed to see its representatives immediately after the St Marylebone parking-meter inquiry report had been issued, and after he had taken his decision on that report He had, however, indicated that no extension of parking meters would be made until the Marylebone scheme had had a full trial and until after he had had discussions with the Association

COORDINATION OF THE PROFESSION

Intraprofessional relations and the coordination of the profession, in the light of what was described as "the coming medicopolitical storm", loomed large in the minds of representatives They approved a resolution, moved by Dr J G M Hamilton (Edinburgh), instructing council to consider "as a matter of urgency" specific arrangements necessary to achieve the "pressing need to improve intraprofessional relationships and solidarity"

Introducing the report of the committee on professional coordination, Dr Wand described coordination as something which proceeded by evolution rather than by edict and dictate "We are a democratic institution in a profession where there are many democratic institutions A year ago there were dark clouds in the sky so far as medical unity was concerned It is my belief that those clouds are dispersing" He referred particularly to the setting-up of the review committee

A motion from Lincoln welcomed any action which would promote unity on matters affecting the general welfare of the profession Dr A. M Maiden explained that it was intended that every avenue of approach to the non-politically-minded practitioner in the periphery should be explored

Mr A Lawrence Abel (Marylebone) said it was clear that some action must be taken by the Association to promote unity "Those of us who are not perhaps quite anæsthetised by the Royal Commission will wake up to the fact that we must have every member of the profession in contact with every other," he declared Here was a great chance for the Association to carry out rehabilitation, to make sure that those young men aged 65 who had retired from the service on July 5 were allowed to wear out and not to rust out "I have estimated that if 20 of these young men were employed and provided with a morning coat and top hat, and given travelling expenses, they could visit every doctor in the country who does not attend a B M A meeting—and that is quite a fair proportion" Dr Wand invited any doctor to write to the secretary with positive suggestions

TELEVISION PROGRAMMES

Dr G S R Little (Greenwich and Deptford) declared "I do not think we did good by suggesting that the *Your Life in Their Hands* programmes were a cheap form of entertainment In the main, as many of you must know, they were very good and they did not produce any adverse reactions At least we did not have evidence that they did" He warned the meeting that the public were apt to look on the profession with disfavour "when we batten down and blow cold over things of this nature"

Dr Wand owned that "we may have to review our ethical approach to these developments, which are bound to take place and are taking place in other parts of the world, particularly in the North Americas"

Dr Doris Odlum (Bournemouth) felt strongly that the new medium was a tremendous power for good or evil It quite obviously appealed to the public as a means of education and a source of information There should be such an active relationship with the B B C that the Association could go to them and say they thought a particular programme would be of great value "I hope that we shall not be so conservative as to give the impression that we are hostile or trying to put back the clock."

Harrow withdrew a motion calling on the B B C to consult with the B M A before televising or broadcasting programmes "which are liable artificially to increase the work of doctors and cause anxiety in the population at large"

CANCER EDUCATION

East Yorkshire asked the representative body to deplore the use of television for the purposes of cancer education Dr K W Beetham said the small number of active cancer educators concentrated on the 30% of neoplasms, that could be cured and ignored the lethal neoplasms which were 70% this was not education "If we are not in a position to tell all the facts, then quite clearly our profession should not tell any of the facts," Dr Beetham declared Now 8 million people had had thirty minutes' intensive cancer education from the Christie Hospital, Manchester Some thousands, perhaps hundreds of thousands, might for some time have a mild cancer phobia and some might be more permanently affected

Dr G Cormack (Newcastle upon Tyne), however, had no doubt that education, by and large, was a good thing Why should one oppose the public education of the people on a matter of extreme importance to health? Family doctors were always deploring the late arrival of patients with cancers which could be cured He suggested that the B B C and Independent Television contractors should not only educate about cancer but discourage cancer neurosis at the same time The East Yorkshire motion was defeated

SPENS A CASE FOR THE SCOTTISH COURTS?

The contractual validity of the Spens reports may after all be tested in the law-courts Dr Wand recalled that a resolution of the Conference of Local Medical Committees in June last year caused the council of the Association to explore the possible difference between Scots and English law in relation to this The opinion of Scottish counsel had been taken "The Association has been advised that in Scotland there exists a procedure known as a 'special case' which is particularly apt to raise the question which we wish to have decided by the courts It differs from the usual type of contentious litigation in that the parties amicably agree to present their differing views of the position to the Court for objective decision"

In order to raise a special case it was necessary, in the first place, to have the consent of the Secretary of State for Scotland, as the Minister responsible for the National Health Service in that country, thereafter it was necessary for the Association and the Secretary of State to agree upon a statement of facts and a question or questions of law to be submitted to the court "Both the statement of facts and the questions of law we propose will be so framed as to ask the court to determine whether our view or that of the Government regarding the obligations implicit in the acceptance of the Spens report and the Danckwerts adjudication is correct"

The Minister of Health and the chairman of the Royal Commission had been informed of the Association's decision to seek the agreement of the Secretary of State to the presentation of a case, and the matter had been laid before the Secretary of State

ANONYMITY

Dr C P WALLACE (Guildford) said the Association still intimidated and prevented learned members of the profession from giving information to the public "I can see nothing unethical, immoral, or improper if Mr Lawrence Abel—so well known and highly respected in the representative body—were to address the public on cancer," he continued, "yet, according to the ethical rules of the Association, that would be out of order"

The new chairman of the central ethical committee, Dr S NOY SCOTT, announced that the committee at its next meeting was, at his request, to reconsider anonymity on television

HOSPITAL STAFFING

Mr T HOLMES SELLORS, chairman of the Central Consultants and Specialists Committee, told the meeting of an estimate that there were between 100 and 110 senior registrars in each of the specialties of general medicine and general surgery who, being time-expired, now constituted a group of people who could not be employed although fully equipped in nearly every case for consultant work The Ministry had persistently refused to accept the principle, laid down in the Strachan report, that there should be a review to decide whether hospitals were adequately staffed Instead the Minister had imposed his own attempted solution—the creation of a special type of post to be determined by the regional hospital boards where they felt there was a vacancy for a man doing such advanced work and who could not find a suitable appointment in it "The Central Consultants and Specialists Committee and the Joint Committee have rejected that idea completely as being mere stalling for political expediency," declared Mr Holmes Sellors "The only suggestion of the Ministry which has been accepted as providing a loophole to continue negotiations is the formation of a working party which has as its terms of reference 'to study the whole of hospital staffing'"

The management side of Whitley Committee B had agreed to consider cases of S H M O s doing consultant work Over 10,000 letters had been sent to S H M O s, nearly 1000 replies had been received, of which 500 had been selected as suitable cases to place before the management side for discussion "There is, however, the disconcerting feature that it appears the management side had no idea that the problem was so extensive, and they have quickly reverted to their original terms—that they would look at such cases and see what the nature and size of the problem was, but would not commit themselves any further as to what they would do with them"

Dr C VIPONT BROWN (Manchester) spoke of an aspect of the problem of hospital staffing which was of particular concern to general practitioners Outpatient departments should be regarded as consultative clinics, but in many cases the patients were not seen by consultants The fact that other members of hospital staffs were doing work of consultant status emphasised the need for the creation of more consultant posts

Dr N K SHINTON (Birmingham) proposed a motion deploring the decision of the Minister of Health to create designated senior registrar posts before the recommendation of the working party had been made

Mr H H LANGSTON (Winchester) asked whether the junior hospital staffs group council would be prepared to advise members in no circumstances to apply for these posts Mr R BREARLEY, chairman of the group council, said that he would be prepared to advise such a course of action, and he believed his executive committee would endorse it Mr LAWRENCE ABEL moved an addendum instructing council to refuse advertisements for these posts This was accepted as a reference to council, and the original motion was carried

Also carried was a motion from Birmingham urging speedy action "so that S H M O s whose level of work and responsibility in their present post can be shown to be of consultant standard may be paid as consultants"

DISTINCTION AWARDS

Dr WALLACE, advocating the publication of merit awards, thought that the council seemed unaware that the present method of distinction awards was unacceptable to the profession and contrary to public policy, and he did not feel that the Central Consultants and Specialists Committee could approach the matter with that lack of bias which it demanded On the other hand Scotland, according to Dr A SMITH (Lanarkshire), was well satisfied that the system operated satisfactorily and that publicity would be very wrong

Dr H GLYN JONES (Bromley) thought that if there were within the State service people of such ability that they merited very special awards, they should be known to general practitioners, the people who would refer cases to those consultants

Dr J C KNOX (Tyneside) claimed that the Central Consultants and Specialists Committee did not know what the consultants wanted The consultants in his region felt quite as strongly as the general practitioners about this secrecy His division believed that when the profession had been hesitating whether to enter the Health Service in 1948, information had been divulged by the Minister about who would be getting the merit awards and that had influenced the committee to lead the profession into the service Mr J R NICHOLSON-LAILEY (West Somerset) said it would be grossly unfair to pillory the consultant who had not a merit award The general practitioner knew far better than any merit-award committee who was a good consultant

The debate was cut short by a motion to put the question Mr Holmes Sellors said it was early realised that publication was absolutely impracticable, and he pointed out that consultants in the periphery were able to express their views Dr Wallace held that it was impossible to imagine that it was in the public interest that public money should be dispensed at the instance of a secret committee to secret people He suggested that a secret ballot of consultants and specialists would overwhelmingly throw out the system

After a count, the meeting supported Dr Wallace by 96 votes to 91

NATIONAL MAJOR CASUALTIES SERVICE

Mid-Cheshire asked the meeting to state that it was "not satisfied with the complacency of the council regarding the national major casualties services" Dr W N Leak said "Much has been done in recent years to organise rescue work, but apart from the Didcot disaster, where affairs were chaotic, all have occurred in well-populated areas, where help and hospital were readily available It would, I fear, be very different if a disaster occurred—as it inevitably will in time—in a rural area far from hospital help In such conditions careful planning beforehand may save many lives, but of this planning general practitioners had so far have no indication"

Dr R Smith (S Middlesex) drew attention to the fact that near London airport were the homes of half a million people, who were exposed to the constant menace of disaster from the air The regional hospital board had a plan, but applied to the London airport area it ignored the fact that on the spot in this densely populated area there was already a mobile force of general practitioners —not one of whom would know where to start if he found himself suddenly near the scene of an air disaster The population at risk increased steadily with the development of new housing estates

Dr R. L Meyrick (Lewisham) opposed Mid-Cheshire's view "We had a major disaster last year," he said, "and the arrangements worked with complete satisfaction" The Mid-Cheshire amendment was lost

CONSULTANTS IN TRAINING AND GENERAL PRACTICE

Arrangements for hospital junior medical staff to obtain experience in general practice during their hospital employment should be left to the individual hospital, Marylebone considered Dr E C Warner remarked that it was not only the consultant in training who should have experience in general practice but anybody who would play a part in the medical life in this country

Dr R M S McConaghey (Torquay) thought there was nothing better for harmony in the profession than that each person should have a spell of doing the work of the others

Dr G S R Little (Greenwich and Deptford) did not think it should be left to the individual He was going to specialise, he did not then realise the value of experience in general practice

The Marylebone motion was carried

DEFICIENCIES OF HOSPITAL BUILDINGS

Dr H G H Richards proposed a motion, which was adopted, instructing council to press the Ministry to allocate substantially greater sums to capital development in relation to hospital services "Hospital building in the non-teaching institutions remains the Cinderella of the public service," he complained Out-of-date buildings made for excessive staffs of all types

Dr H Scott-Kerr (Gloucester) recalled that when the National Health Service started the Government of the day promised a full medical service With waiting-lists of three months to two years, the public had been hoodwinked

This point was elaborated by Dr E A Gerrard (Manchester), who said "The position represents nothing less than a public scandal" 4 people were waiting for every teaching-hospital bed in London and 5 for every such bed in the provinces In gynæcology 9 patients were waiting for every bed "In the Middlesex Hospital there are 16 women waiting per bed, in Cardiff 19, in Cambridge 21, and in St Mary's Hospital, Manchester, no less than 26 For a pelvic-floor repair they have to wait from three to four years to come in, at the Middlesex it is two years, in Cardiff three, and in Cambridge three and a half We have had new offices and flats, and particularly new Government offices, and new schools We are of course desperately short of money in this Welfare State, but even so is it fair that little Johnny should attend a diamond-studded school and his mother have to wait three to four years to have her prolapse repair? In my view it is absolutely crazy"

CENTRAL POOL

Dr A B Davies, chairman of the General Medical Services Committee, made a statement about the final settlement ("I really mean supplementary payment, because there is no such thing as a final settlement until our claim has been met," he remarked) For 1956–57 the final settlement was £4,600,000 One reason why it was less than in the previous year was inflation of lists, for the first time total numbers were greater than the total population In addition doctors had received a greater amount of money direct from Government sources Nevertheless, when the total figure was added together, in the past year general practitioners had received the highest total sum on record The timing of the payment had been improved from December in 1956 to June in this year

Bristol demanded a change in the working of the central pool, "which is proving to be unjust and discouraging in its effects" Dr A G Heron described it as a system of merit penalties, general practitioners as a whole could not earn any more, however hard they worked or however much extra work they took on

Dr Wand said that if one had a pool which allowed for an average income for every practitioner, as laid down in Spens, and if, as the Danckwerts award provided, every practitioner coming into the service provided extra money to be divided, then one could not have it both ways On the question of vaccination, he had not heard a speaker point out that general practitioners might have less work to do as a result of such vaccination "With all its faults —and no system is perfect—the pool system has done us well," declared Dr Wand

Bristol's motion was lost

REJECTION OF FURTHER INTERIM AWARD

In a reference to the refusal of the Minister of Health to grant a further interim increase since the Royal Commission had not reported, Dr A M. Read (Portsmouth) commented "We have long since discovered that a gentleman's agreement with a politician is a contradiction in terms" (Applause) Dr R P Hendry (Rugby) remarked that the profession's claim had been given top-priority procrastination treatment

The question was put "That this meeting wholeheartedly supports the council in making continued efforts to secure a further interim increase in remuneration" Dr A Talbot Rogers, deputy chairman "That is passed without a single opposing vote"

SCHEMES FOR WITHDRAWAL

Dr Davies announced that a special subcommittee had been appointed to deal with the matter of schemes for withdrawal from the National Health Service, and an impartial non-medical expert of the highest eminence had been engaged It was hoped to report in good time before the Royal Commission reported

GENERAL-PRACTITIONER BEDS

The meeting passed a motion on the need for more general-practitioner obstetric and medical beds, after rejecting an amendment to delete the reference to medical beds Dr F S Catto (Manchester) attacked Lord Moran's House of Lords suggestion that access should be restricted to certain general practitioners "I believe that every general practitioner ought to have access to these beds," he said "If not, who is to select the general practitioners?"

PERSECUTION OF DOCTORS

The meeting was told about persecution of doctors in Cuba Dr R L Luffingham (East Yorkshire) said that what the Cuban delegation had described to the World Medical Association had been confirmed Doctors in Cuba had been imprisoned for treating patients with views against the dictatorship, some had been beaten for refusing to disclose information, and armed police were placed outside doctors' surgeries President Baptista had not replied to a request from the World Medical Association to send independent observers The representative body carried an amendment making clear that it accepted the facts reported

MEDICAL WAR CRIMINALS

Dr Eric Townsend (Cornwall) moved

"That this representative body expresses its deep distress on learning that the Federal German medical authorities have seen fit to permit the reinstatement of a practitioner guilty of medical war crimes It instructs council to take whatever steps seem practical and effective to bring the views of the British Medical Association to the notice of those responsible for this cynical affront to the honour and high ideals of the true practice of medicine throughout the world"

Dr Townsend said that Dr Herta Oberheuser, a young fanatical Nazi doctor who volunteered to go to the notorious Ravensburg concentration camp, selected women for experiments by inflicting wounds and then deliberately infecting and neglecting these wounds She admitted that many of her patients died as a result of these experiments In 1947 she was sentenced to twenty years' imprisonment Her sentence was reduced in 1951 to ten years In 1952 she was released She had gone into practice near Hamburg

She was not alone Hans Eisele, from Buchenwald, was also again in practice Hans Bodo Gorgass, who in experiments on euthanasia killed thousands of victims in mental hospitals and who was sentenced to death but reprieved, was also in practice

Dr I H Milner (City) recalled that 23 S S physicians and scientists appeared before the U S Military Tribunal No 1 in Nuremberg They included Karl Gebhardt, head of the German Red Cross, and Herta Oberheuser 15 were found guilty, 7 were sentenced to death, 5 to life imprisonment, and Herta Oberheuser, the only woman, was sentenced to twenty years' imprisonment She had been "rehabilitated" and given a position of responsibility She admitted having herself administered injections of petrol to patients "Allowing this physician to practise places us in an invidious position in regard to members of the medical profession in Germany," declared Dr Milner

Dr I D Grant, chairman of the international relations committee, said that the committee had written to the Bundesarztekammer, and he read the reply it had received

"We German doctors deplore the fact that we have not the legal right in the Oberheuser case to withdraw permission to practise The Federal Chamber of Doctors has taken every step within the ambit of the law to prevent the practice of medicine by Dr Oberheuser" The Ministry of the Interior of Schleswig-Holstein had now instituted proceedings for the withdrawal of the approbation, and the German medical profession hoped that the withdrawal of the approbation would be pronounced and that the right to practise medicine would be taken away from Dr Oberheuser

Dr Grant added "Like everyone we are filled with horror that this woman should have been restored to the practice of medicine in Germany or anywhere else"

Dr Townsend asked permission to delete the words "Federal" and "medical" from the resolution As amended the resolution was carried without dissent

INDUSTRIAL COURT AWARD

Dr J B Tilley, chairman of the public-health committee, referred to the judgment of the Industrial Court that public-health doctors should be considered as part of the local-government hierarchy, and their salaries should not be considered in isolation, and that this was without prejudice to any claim that might be made by public-health doctors after the claims of all other local-authority officers had been settled "It is most satisfactory that the Industrial Court should have made pronouncement of this kind on a matter on which were not asked to give any opinion," he said The bility of the Whitley machinery breaking down was real

FULL-TIME SERVICE SOMETIMES?

Dr A J Macleod (Outer Isles) wanted an ad the motion from Harrow, moved by Dr J B Wrath Rowe, that the meeting was strongly opposed to a wh time salaried National Health Service, making it that this was "for general practice as a whole, with prejudice to what may be for the best in limited The Chairman did not ask for a vote on either motion amendment "I put it that we reaffirm our policy," h said The meeting agreed

PRESCRIBING IN GENERAL PRACTICE

Despite assurances from Dr Davies, several spoke in favour of a motion by City that the council should inquire into the whole question of freedom of prescribing in general practice Dr Alan Rezler said that every year hundreds of warning letters were sent to doctors, about

700 doctors were seen by regional medical officers, and a few were fined, some heavily "We wonder how many patients are sent to hospital solely to save the costs of prescription," he remarked "I suggest that the present freedom to prescribe is freedom to enter the field 'but beware of the bull'"

Dr B BURNS (Sheffield) declared that the much-vaunted freedom for prescribing was illusory In hospital even the most junior doctor, unlike the general practitioner, had carte blanche But Dr J S M ORD (Glasgow) opposing the motion, which was lost, thought younger men must be guided

TRANSFER OF PATIENTS

A motion that restrictions on the transfer of patients should be abolished was defeated Dr COLIN RUSS (C[illegible]) moved it Arguments in favour of the motion were that restriction encouraged complaints, and that the National Health Service patient should not have to ask permission, any more than a private patient had to

"MERIT AWARDS" IN GENERAL PRACTICE

Dr WAND appealed to the representative body to give guidance as to whether it wished a system of "merit awards" for general practice to be considered He explained that the Association had been asked by the Royal Commission to give consideration to some kind of incentive award

To obtain an expression of views, Dr R M S McCONAGHEY moved "That this meeting sees no objection to a 'merit award' system for general practice, providing a practicable scheme can be devised and subsequently approved by the representative body" An attempt to make this motion read that there was no objection to "an alternative method of remuneration" was greeted with cries of "No," and by a large majority the motion was approved

ELECTION OF G M C MEMBERS

Approval was given to the new method of selecting the Association's candidates for election as elected members of the General Medical Council The recommendation provides that a "postcard whip" sent to all doctors shall contain the names of every candidate seeking election, but with the names of those supported by the Association printed in heavy type

A I D

In the last two hours of an extended final session there was a long and rather emotional debate on artificial insemination by donor, a matter on which the platform appealed for guidance from the meeting

Dr L S KEENAN (Harrow) condemned any form of artificial insemination as unnatural Dr F W BELAM (Guildford) was opposed to artificial insemination by donor but not by husband Said Dr K M TOMLINSON (Gloucestershire) "To help one unhappy woman does not justify our help in the introduction of an almost certainly unhappy child" But Dr A BARKER (council) knew there had been a great deal of happiness in the right cases

Eventually the representative body resolved, while making no pronouncement on the non-medical aspects of A I D, to authorise the council to submit evidence to the Government committee on this subject, from the medical point of view, if so desired But it had already voted 101 in favour to 84 against an amendment by Dr C P WALLACE (Guildford), expressing "grave concern at the increasing practice of A I D"

Special Articles

AN EVALUATION OF TREATMENT OF DEPRESSIVE ILLNESS IN A DAY HOSPITAL *

MICHAEL CRAFT
M.D Lond, M R C P E, D.P M

LATE REGISTRAR, BETHLEM ROYAL AND MAUDSLEY DAY HOSPITALS, DEPUTY SUPERINTENDENT, ROYAL WESTERN COUNTIES HOSPITAL, STARCROSS, DEVON

DAY-HOSPITAL treatment in psychiatry was first described by Dzaghagarova (1937) and Dzaghagarova and Balabanova (1944) in Russia and by Cameron (1947) in North America These and subsequent articles have emphasised its cheapness and suitability for those of the mentally ill who are well enough to travel and spend nights at home

It has been suggested that day hospitals, by intensive treatment, may diminish the duration of such treatment in mental illness (World Health Organisation 1953) Be that as it may, it seemed desirable to compare the results of day-hospital treatment with those of conventional hospital care To this end three studies of Maudsley Hospital records were made Since depressive conditions form the bulk of those treated, it was decided to concentrate on them

The working of the Maudsley Day Hospital has already been described (Harris 1957) It admits only those who, but for the day hospital, would have needed inpatient admission

First Study

The first study concerned patients with depressive states who had had previous attacks of depression, for which they had been treated as inpatients In three years of Maudsley day-hospital practice 57 such patients were found In 5, however, the inpatient treatment had been recent—within twelve months—and it was thought that the two periods of treatment might have been for the same illness which had incompletely remitted 8 patients had had both day-hospital and inpatient treatment for the same attack, and in 3 further cases either information was inadequate or the illness was not depressive These 16 patients were excluded

In the remaining 41 patients the duration of day-hospital treatment was longer in 11 and shorter in 30 than the duration of mental-hospital treatment of their previous depressive illnesses The average for the 41 inpatient periods was 106 7 days, and that for the 41 day-patient periods 68 0 days The difference between these averages is similar to that obtained in another series discussed below and is explainable in almost identical terms In each case it was the earlier depressive episode which was treated on conventional inpatient lines Also the earlier attack may have been more severe There is conflicting evidence in the literature about the extent to which these factors would cause bias in the results

Second Study

The second study was based on female patients with depressive illnesses who completed treatment under the same physician as either inpatients or day patients in the three years ended May 4, 1956 The diagnoses were

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* Abridged from thesis accepted by London University for the degree of M D The first part of this thesis is to appear in the *American Journal of Psychiatry*

neurotic depression, depressive phase of manic-depressive psychoses, involutional melancholia, and puerperal depression. Patients staying less than a week, those treated as both day patients and inpatients, and those receiving additional diagnoses of personality disorder, organic cerebral illness, or brain damage were excluded. Detailed notes of the initial outpatient attendance and other examinations on admission were available, and these were used to assess the depth of depression on admission on the following four-point scale:

Grade	*Retardation*	*Somatic disturbance*	*Registrar's comment*
(1) Mild	Nil	Minimal or none	Need for admission doubted
(2) Non-psychotic	Moderate	Poor sleep, early waking, some anorexia	Standard admission
(3) Psychotic	Severe	Severe insomnia, early morning depression, loss of weight	Seriously ill patient
(4) Stuporose	Mute	Stupor	Bed patient

For a retrospective series, previous rating-scales proved difficult to apply (Rowell 1951, Cohen et al. 1944, Lorr et al. 1951, Meyer 1951, Malamud and Sands 1947). The four-point scale worked well in the circumstances. Groups of day patients and inpatients with illnesses of similar severity were then compared as regards the time taken for recovery. 64 day patients and 69 inpatients, with depressions of similar severity on admission, were stated at discharge to be "recovered." 49 of the former and 38 of the latter were discharged within three months of admission, and it can be shown by χ^2 that this is a significantly greater number of day patients than inpatients where $0.02 > P > 0.01$. Day care is here again shorter than inpatient care.

Third Study

For the third study it was decided to form matched pairs of female depressives, each including one day-hospital patient and one inpatient. 43 pairs were matched for age, previous mental-hospital admissions, severity of illness by the four-point scale on admission, marital status and social class. The characteristics to be matched were decided on after perusal of twelve authors which proved the most helpful in assessing prognostic factors (Bond 1954, Dedichen 1946, Harris and Lubin 1952, Karagulla 1950, Lewis 1936, 1938, 1944, Lundquist 1945, Malzberg 1929, 1935, 1940, 1954, Ødegaard 1954, Pollock 1925, 1931, Rennie 1942, Robins 1954).

As an additional check regarding the depth of depression, the physician who had had charge of the patients was asked to rate the 43 pairs of notes according to the scale of severity. By χ^2 there was no significant difference ($0.5 < P < 0.3$) between his results and mine.

It was not possible to match for duration of illness before admission. 27 day patients and 31 inpatients had symptoms for less than six months before admission. Using χ^2 this was not significant at the 5% level. 25 day patients and 22 inpatients received electroconvulsion therapy, this difference also not being significant.

The results of treatment for the series were assessed by three criteria—length of stay in hospital, degree of recovery on discharge, and condition five months after discharge. The average duration of treatment of the day patients, together with their standard error, was 73.0±7.2 days, and of the inpatients 101.6±12.3 days. A direct comparison of these averages by the *t* test shows that P is just 5%. The statistician analysing the results felt that this figure was not significant, because the 5% level was only just attained and the spreads of the distribution being compared were most significantly different ($P < 0.001$), the *t* test being of doubtful validity in these circumstances.

The difference in the scatter of the results was almost entirely due to three high values for the inpatients. If these three values are deleted (and it is dangerous to discard observations unless there are strong external reasons for so doing), the remaining 40 inpatients give an average of 84.7±8.3 days. The comparison of this result with the 43 day patients, allowing for the different numbers, gave a value of P between 0.25 and 0.30. This is not significant.

Similar statistical arguments apply to the figures given in the first study for a different group of patients. Though the significance of the apparently shorter stay of the day patients is therefore doubtful, it is quite clear that *day treatment does not take longer than inpatient treatment.*

Degree of recovery with the matched series showed 26 day patients recovered at discharge compared with 28 inpatients, 14 day patients and 14 inpatients improved, and 3 day patients and 1 inpatient unchanged or worse. By χ^2 P lies between 0.8 and 0.7. This is not *significant.*

A follow-up was undertaken by personal interview five months after discharge and was successful with 41 day patients and 41 inpatients, 95% of the total. Within the five months 2 day patients and 4 inpatients had needed readmission to hospital. This difference is not significant. At the end of five months 30 day patients and 31 inpatients had returned to their previous output of work, whereas 11 day patients and 10 inpatients had reduced output. This also is not significant. Clinical rating-scales showed that at five months 23 day patients and 27 inpatients maintained recovery, 9 day patients and 7 inpatients remained improved, and 7 day patients and 6 inpatients were unimproved. Information was inadequate for 7 patients. By χ^2 P lies between 0.7 and 0.5, and there is no significant difference.

Comment

These retrospective studies can be criticised on the ground that the day hospital is most suited to manage the milder depressive illnesses and there would be a strong tendency for admitting physicians to forward the less-seriously ill for treatment. One might infer from this view that the milder illnesses would more rapidly recover. Only a trial with initial random allocation of patients would completely satisfy this criticism. It was to deal with this point that the rating-scale and the matched series were set up and an independent assessment was made of the severity of illness. It is felt that, so far as was possible, cases of equal severity were compared. In this context, however, it is worth noting that important studies by Rennie (1942) and Lundquist (1945) doubt whether there is a significant relation between depth of depression and duration of stay or outcome.

Summary and Conclusions

Three studies of Maudsley records are presented which indicate that many depressive illnesses were as effectively treated in the Maudsley day hospital as in the wards, judged by length of stay in hospital, degree of recovery on discharge, and a five-month follow-up. There is evidence that treatment in the day hospital shortens the length of stay in hospital.

I am indebted to Prof. Aubrey Lewis for his encouragement, to Dr. Arthur Harris for his help and permission to use the clinical material of the Bethlem and Maudsley Day Hospitals, and to Mr

Frank Downton and the late Dr Vera Norris of Leicester and London Universities for their statistical advice

REFERENCES

Bond, E D (1954) *Amer J Psychiat*, 110, 561
Cameron, D E. (1947) *Med Hosp* 68, 60
Cohen, L H., Malmo, R. B , Thale, T (1944) *J gen Psychol* 30, 65
Dedichen, H H (1946) *Acta psychiat , Kbh* suppl 37, p 3
Dzhagarova, M A (1937) *Nevropat i Psikh* 6, 137
— Balabanova V K. (1944) Day Hospitals and the Mentally Ill Moscow
Harris, A. (1957) *Lancet*, i, 729
— Lubin, M (1952) *Mschr Psychiat Neurol* 124, 126
Karagulla, S (1950) *J ment Sci* 96, 1060
Lewis, A. (1936) *ibid* 82, 488
— (1938) *Brit med J* ii, 875
— (1944) *J ment Sci* 90, 256
Low et al (1951) *J clin Psychol* , 7, 260
Lundquist, G (1945) *Acta psychiat , Kbh.* suppl 35
Malamud, W , Sands, S L. (1947) *Amer J Psychiat* 104, 231
Malzberg, B (1929) *Psychiat Quart* 3, 590
— (1935) *Ment Hyg , Concord*, 19, 449
— (1940) Social and Biological Aspects of Mental Disease. Utica, N Y
— (1951) *Psychiat Quart* 28 398
Meyer, B (1951) *J clin Psychol* 7 250
Odegaard O (1954) *Ment Hyg , Concord*, 38, 447
Pollock, H M (1925) *ibid* 9, 783
— (1931) *Amer J Psychiat* 11 1037
Rennie, T A C. (1942) *ibid* 98, 801
Robins, A J (1954) *ibid* 111, 434
Rowell, A (1951) *J clin Psychol* 7, 255
World Health Organisation (1953) *Tech Rep Wld Hlth Org* no 73

LEPROSY RESEARCH FUND

This Fund, which is sponsored by the American Leprosy Missions, was founded in 1953 with the aim of linking leprosy to general medicine and to fundamental research and so attracting more workers to this important but neglected specialty To administer the Fund, but not to raise funds a committee was set up in England, of which Dr W A R Thomson is chairman and Dr R G Cochrane secretary

The Fund has not the money to finance large projects or research schemes, and its limited resources have been used to stimulate pilot research projects to test whether a particular problem is of sufficient importance to warrant asking for the backing of one of the large Foundations The Fund is in touch with many institutions all over the world, and also arranges small clinical trials of new drugs to collect preliminary data before comprehensive trials are launched

Projects which the Fund has backed during the past five years include the following

Dr Graham Weddell, with a grant from the Fund, visited India in 1951 to investigate the possibility of using leprosy as a tool in the research of cutaneous sensibility As a direct result of his work, Dr David Jamison was appointed, in 1957, to a research fellowship sponsored by the Royal Society, to undertake more detailed research in the histopathology of leprosy, with particular reference to cutaneous sensibility

In 1955 the Fund raised the money for Dr E M Brieger of the Strangeways Laboratories, Cambridge, to visit the African Inland Mission Hospital at Oicha in the Belgian Congo to investigate the possibility of using electron microscopy in the study of the life history of the *Mycobacterium lepræ* The value of this investigation is shown by the fact that the Colonial Medical Research Council has now given a grant for Dr Brieger s work

The Fund proposes to organise a reference laboratory and a registry of histopathology which will ultimately contain complete clinical, photographic, and histological records of types and groups of leprosy in the different parts of the world The cost of organising this unit will be about £2300 a year

The address of the Leprosy Research Fund is 11A, Weymouth Street, London, W 1

> " Honest compassion has no coefficient in the world of statistics—at least up to now An unreliable guide to policy on its own, it nevertheless has the loudest voice and draws the warmest cheers I suppose the majority of young parents would prefer that a million mentally disordered people were permanently ' locked up ' than that harm should befall their children The development of civilised society has always depended on the extent to which considerations of that kind can be subordinated to the common good ' —C H ROLPH, *New Statesman*, July 5, 1958, p 6

Public Health

OCCUPATIONAL HAZARDS IN THE BONE-MEAL INDUSTRY

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BONE fertiliser is a well-known source of anthrax infection in animals and occasionally in man In Greenock there is a factory which produces animal charcoal for use in sugar refining This factory imports bones from India, Pakistan, and the Argentine As delivered these bones have already been broken up into fragments varying in size from 2–3 in long to granules about $^1/_4$ in in diameter The raw bones are further broken up in crushing mills, and thereafter the crushed material is passed over moving metal screens which sort it into three grades of granularity before it is reduced to charcoal in the ovens

The very fine bone dust remaining at the crushing mills is collected and sold as bone fertiliser Precautions against inhalation of this fine dust include the provision of face masks for the workers and the use of exhaust fans erected over the crushing-plant. The workers wear protective clothing, but the fine dust penetrates through this clothing and reaches the underclothing Bone dust is to be found everywhere in this factory, even in the offices

This description of the heavy concentration of bone dust is important, because frequent sampling of the raw bones, the crushed bones, and the bone dust has shown that the spores of virulent anthrax bacilli are present Such sampling has only been carried out over the past five years, during which cases of cutaneous anthrax have occurred among the workers An official of this firm assures me that the source of supply of bones has been the same in the past twenty-eight years Further, the only cases of cutaneous anthrax he has knowledge of are the four described here

Apart from cutaneous anthrax I have encountered two cases of empyema in workers in this factory In both cases the infecting organisms were of the clostridial group These patients were employed at the crushing mills and were therefore exposed to heavy concentrations of bone dust

Cutaneous Anthrax

Table I shows the age, sex, and occupation of the four patients with cutaneous anthrax

TABLE I—DATA ON FOUR CASES OF CUTANEOUS ANTHRAX

Case no	Sex	Age (yr)	Occupation	Site	Date admitted
1	M	29	Labourer	Side of neck	Dec. 1955
2	M	47	Lorry driver	Back	April 1956
3	F	53	Sack repairer	Over rt breast	Nov 1957
4	M	29	Process worker	Rt malar eminence	March, 1958

Case 1 —This man, aged 29, was admitted forty-eight hours after a painless red papule had appeared on the left side of his neck. He was a labourer employed in carrying sacks of raw bone fragments to the crushing mill, he stated that he carried these sacks over his left shoulder It was likely then that either he had an abrasion on the left side of his neck or an abrasion was produced by a spicule of bone protruding through a sack

On examination the sore had a black necrotic centre about 1/4 in in diameter There was much swelling of the tissues around this sore and regional adenitis Smears of serous exudate taken from this sore were positive for *Bacillus anthracis* The patient was afebrile and non-toxic

Treatment and progress—Phenoxymethylpenicillin 125 mg was administered six-hourly The lesion enlarged for two days, reaching a maximum size of 2 in × 5/8 in , around the necrotic centre a ring of vesicles appeared After three days the lesion began to regress The patient was discharged after fifteen days He was seen after twenty-eight days as an outpatient when the sore was granulating, but it was obvious that a scar would result

Case 2 was a lorry driver, aged 47, who delivered sacks of bone meal from the factory, loading the sacks on to his back from the tailboard of the lorry He was admitted with a forty-eight hour history of pain and swelling over the left side of his back On the day of admission he felt nauseated and shivery and had to go to bed

On admission he looked very toxic, and his blood-pressure was 80/50 mm Hg, temperature 104°F The sore consisted of a black necrotic centre about 1/4 in in diameter, and there was much lardaceous œdema surrounding it for a radius of 8–10 in , with gross hæmorrhagic infiltration into this œdematous zone The sore spread for seven days and the hæmorrhagic infiltration became more extensive

Treatment and progress—Phenoxymethylpenicillin 250 mg was administered six-hourly After three days the patient became afebrile and his general condition was much improved He was discharged after twenty-eight days with a deep ulcer where the eschar had separated

Case 3 was a woman, aged 53, employed as a sack repairer, before the sacks were submitted to her for mending they had been cleaned by vacuum suction Five days before admission she noticed a pimple over her right breast On the day of admission she became collapsed and dyspnœic

On admission she obviously had severe peripheral circulatory failure, the blood-pressure was not recordable The sore was typical of a malignant pustule, there was much œdema and hæmorrhagic infiltration over the right breast

Treatment and progress—In view of the circulatory failure an intravenous saline drip containing noradrenaline was set up, and intramuscular crystalline penicillin 250,000 units six-hourly was administered After twenty-four hours there was no improvement in peripheral circulation, and although the serum-potassium and serum-sodium levels were normal it was considered advisable to replace the noradrenaline by hydrocortisone Despite this change extreme peripheral failure persisted for sixty hours, during which the blood-urea rose from 81 to 108 mg per 100 ml Thereafter she began to improve, but, as in the other cases, there was some extension of the lesion for the first three to four days After nine days a secondary sore appeared some 3 in below the anthrax sore, this sore consisted of a blood-filled vesicle, and was considered to be a trophic lesion due to the extensive œdema further precipitated by the prolonged hypotension Smears of the original sore were positive for *B anthracis*, but as expected the "trophic" sore was negative Blood-cultures were sterile During her period of peripheral failure she complained of precordial pain, but an electrocardiogram was essentially normal This patient was discharged after five weeks with both sores granulating Scarring is to be expected

Case 4—A man, aged 29, who worked at the crushing mill, was admitted with a thirty-six-hour history of a sore over the right malar eminence He had regarded the sore as a boil, but became worried when his face began to swell On admission he did not look ill and was afebrile The lesion was a typical malignant pustule with surrounding œdema and regional adenitis He was treated with phenoxymethylpenicillin 250 mg six hourly, and the lesion began to regress within twenty-four hours The resultant scar will be small

Clostridial Empyema

Table II shows the ages and occupations of two men in whom empyema due to clostridial infection developed

TABLE II—DATA ON TWO CASES OF CLOSTRIDIAL EMPYEMA

Case no	Sex	Age (yr)	Occupation	Site	Date of admission
5	M	30	Process worker	Rt empyema	March, 1953
6	M	41	Process worker	Lt pneumonia plus effusion	March, 1958

While it seems strange that clostridial organisms should infect previously healthy lungs, I am convinced that this was so in each of these cases Neither patient had any history of chronic or recent pulmonary infection In each case large gram-positive bacilli were seen in large numbers on direct examination of pleural fluid and specimens of sputum

Case 5—A man, aged 30, employed at the bone-crushing plant, was admitted with a ten-day history of right-sided chest pain, preceded by rigors, and of cough which was at first unproductive Six days before this illness began typical herpes zoster had developed over the right side

On admission he looked very ill and his temperature was 102 F Healing herpes zoster lesions were noted in the right hypochondrium The physical signs of a right-sided pleural effusion were present Aspiration of the right chest yielded 16 oz of chocolate-coloured fluid with a glue-like odour Direct examination of this fluid showed large gram-positive bacilli Sputum samples, too, were positive for clostridia Clostridial organisms were recovered on anaerobic culture Later these were identified as *Clostridium tertium*

Treatment was by daily aspiration and instillation of oxytetracycline together with oral oxytetracycline

Progress—Daily examination of the pleural fluid showed a gradual disappearance of the organisms, after seven days no organisms were seen and the fluid was sterile Nevertheless, the fluid persisted for six weeks, and during the last two of these weeks closed pleural drainage was in operation He remained febrile for four weeks, but his general condition improved steadily Chest radiographs showed considerable collapse of the right lower lobe with air and fluid in the pleural space What was reported as air was considered to be gas from the organisms, since the aspiration was carried out carefully with a two-way tap Later radiographs showed improvement, and in eight weeks the only remaining lesion seen on the radiograph was obliteration of the right costophrenic angle The patient was then discharged and is still well

Case 6—A man, aged 44, also employed at the bone-crushing plant, was admitted with a history of an influenza-like illness which lasted for seven days His principal symptoms were severe frontal headache and left-sided chest pain aggravated by movement, deep breathing, and coughing, the cough was productive and sputum rusty There was a previous history of left-sided dry pleurisy twenty years ago

On admission he looked anxious and was dyspnœic and slightly cyanosed The blood-pressure was 130/85 mm Hg There was no evidence of any cardiovascular disease The physical signs of a left-sided pleural effusion were present 18 oz of thin brown fluid was obtained by aspiration of the left chest Direct examination of this fluid showed numerous large gram-positive bacilli

Treatment—In view of the patient's occupation and the experience of the previous case he was treated by oxytetracycline both intrapleurally and orally

Progress—Anaerobic culture of the fluid showed that the organisms were of the clostridial group Further investigation suggested that they might be *Cl œdematiens*, but this was not proved and the organisms have up to the present not been specified A chest radiograph confirmed the presence of pleural fluid, and also showed underlying consolidation of the left lower lobe Specimens of sputum also contained clostridial organisms The patient was febrile for twenty days, but at the end of that time was very much improved After four weeks no further fluid could be obtained by aspiration although a chest radiograph at this time suggested that fluid still remained After nine weeks chest radiography showed extensive opacity over the left lung field, but this was thought to be due mainly to pleural thickening The patient is now considered to be well and only the signs of pleural thickening persist

It is not uncommon to find clostridial organisms in the sputum of patients with chronic pulmonary infection The two patients here described were not suffering from chronic bronchitis; Only one of them had a history of previous chest disease—pleurisy twenty years before The pleural fluids on direct examination showed numerous clostridial organisms Both workers were employed in an atmosphere heavily laden with fine bone dust, which on repeated sampling contained the spores of *B anthracis*, although no specific examinations for clostridial spores were made it is reasonable to assume that such spores could also be present Indeed I have been informed that in investigations of bone meal for anthrax, clostridial growth has to be suppressed before inoculating guinea-pigs (J H C Walker, personal communication) It is remarkable, however, that hitherto no cases of pulmonary anthrax have occurred among the workers in this factory

Summary

Four cases of cutaneous anthrax among workers in a bone-meal factory are described One of the patients had severe peripheral circulatory failure, although there was no evidence of septicæmia

Two cases of empyema presumably due to clostridial infection suggest that such infection may be a further hazard among workers in this industry

My thanks are due to Dr P Browning for identification of *Cl tertium* in one of these patients, to Dr J G Goudie for the bacteriological examinations in the anthrax patients, to the Central Veterinary Laboratory at Weybridge, Surrey, for their reports on the various bone samples submitted for examination for anthrax infection, and to Dr J Ramage of Larkfield Hospital, Greenock, for electrocardiographic examination of case 3

ANTHRAX AND BONE-MEAL FERTILISER

D M GREEN
M D St And
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QUEEN S COLLEGE, DUNDEE

W M JAMIESON
M D St And, M R C P E, D P H
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WE have previously reported anthrax in six patients in whom the infection was derived from bone-meal fertiliser (Jamieson and Green 1955) We expressed the view that bone-meal used in this country should be rendered safe from the hazards of anthrax In February, 1957, the Minister of Health announced the setting up of a committee of inquiry

> "To consider the existing legal provisions concerning the importation of goods infected or likely to be infected with anthrax and the precautions to be taken in connection with such imported goods for the protection of the health of persons and to make recommendations" (see *Lancet* 1957)

Since our last report, we have seen four further cases of anthrax One patient was a veterinary surgeon who contracted the disease through contact with an infected animal The other three gave histories of having handled bone fertilisers, and *Bacillus anthracis* was isolated from samples of bone fibre handled by one of them (case 3)

Case-reports

Case 1 —A farm labourer, aged 28, was admitted to hospital with a typical anthrax lesion on the dorsum of the left hand He had cut the hand 3 weeks before, this wound had healed, but 2 days before admission he had scratched the part again, and this was followed by the development of the typical lesion He had been handling a "commercial fertiliser" which probably contained bone-meal Direct microscopy of material from the lesion showed gram-positive bacilli morphologically resembling *B anthracis* Culture and guineapig inoculation were negative The patient was treated with combined penicillin and streptomycin and recovered completely

Case 2 —A farm grieve, aged 53, was admitted to hospital with a lesion on the right side of neck which was typical of anthrax after the acute phase 3 weeks before, he had noticed a small "boil" on the neck, and this had progressed, causing much swelling of neck and face His own doctor had treated the lesion with penicillin Bacteriological examination was not carried out until his admission to hospital, and, not surprisingly, this was negative, microscopically and culturally, for *B anthracis* The patient recovered fully About the time of developing the lesion, he had been actively engaged in spraying fields with bone-meal fertiliser Samples of the fertiliser were not obtained for examination There had been no animal deaths on the farm

Case 3 —A boy, aged 15, was employed as a nursery-worker He was admitted to hospital with typical anthrax of the left cheek 10 days before he had scratched his face and this was followed by the development of the malignant pustule Microscopical examination of material from the lesion showed organisms morphologically resembling *B anthracis*, but culture and animal inoculation were negative He recovered completely after treatment with combined penicillin and streptomycin This boy had been preparing soil for growing tomato plants, which involved the use of bone-fibre While some of the workers wore gloves for this job, he himself had not done so Four samples of the material used by him were obtained, and *B anthracis* was isolated from three of them

Method of Isolation of B anthracis

The four samples of bone-meal fertiliser consisted of three samples of bone fibre from 1 cwt (112 lb) bags—very dusty material with fibres in it—and one sample of bone-meal from a $1^1/_2$ cwt bag which looked like "meal" with fibrous material The source was either Indian or Argentinian, or possibly a mixture from the two sources The samples were treated in the following manner

The material was shaken up with sterile distilled water (25 g in 100 ml) and after standing for two hours, with occasional shaking, the supernatant fluid ("wash') was heated to 70°C for 10 minutes Pour plates were made of varying amounts in 'Yeastrel' agar, which gives deep colonies of *B anthracis* of typical appearance (A J H Tomlinson, personal communication) The formula for yeastrel agar was as follows

Eupeptone no 2	5 g
Yeastrel	3 g
Agar (Davis)	10 g
Distilled water	1000 ml

Autoclave at 15 lb for 15 minutes to dissolve, make to pH 8 2 Steam 30 minutes Filter through 'Chardin', if necessary adjust to pH 7 6 Sterilise in autoclave at 10 lb for 10 minutes

Cultures were also made in the selective medium described by Pearce and Powell (1951) In one of the samples of bone fibre, *B anthracis* was isolated from the yeastrel agar The strain gave a characteristic appearance in a Craigie tube and killed a guineapig, which showed typical macroscopical and microscopical appearances and a McFadyean's reaction

The remainder of the wash was centrifuged, and half the deposit was injected into a guineapig which had been protected 24 hours previously with polyvalent gas-gangrene containing *Clostridium perfringens* antitoxin 2000 units, *Cl septicum* antitoxin 1000 units, *Cl œdematiens* antitoxin 2000 units, and tetanus antitoxin 500 units

In the case of the three samples of bone fibre, the guineapigs died between 24 hours and 72 hours after injection Animals which died at 72 hours showed typical macroscopical and microscopical appearances of anthrax, and *B anthracis* was isolated from the blood and tissues In two animals which died 24 hours after the injection the necropsy appearances were typical of gas-gangrene infection, but in one of them cultures from the heart blood and site of inoculation gave isolations of *B anthracis*

No isolation was made from the $1^1/_2$ cwt bag of bone-meal by either animal inoculation or cultural methods

The strains isolated were tested in vitro by a plate technique using Evans' ' Sentest ' tablets, and they were all sensitive to penicillin, streptomycin, aureomycin (chlortetracycline), oxytetracycline, and erythromycin

Comment

Since 1952 ten cases of anthrax have been admitted to King's Cross Hospital In four cases there is bacteriological confirmation that the patients had handled infected bone-meal fertiliser, strong presumptive evidence of bone meal as the vehicle of infection was present in a further five, one case was not directly associated with bone-meal The infected bone material was imported These findings may be of interest in view of the Committee of Inquiry presently examining the problem of goods likely to be infected with anthrax

Davies and Harvey (1955) demonstrated *B anthracis* by animal inoculation in 5 (12%) of 41 cargoes of imported bone-meal over 18 months They pointed out that the infectivity for man is probably low since only two cases of anthrax were seen during the 18 months In the present series the patient with whom the bone fibre was associated was not the only person to handle the material, but he appears to have been the only one infected

Summary

A history of having handled bone-meal products was given in three out of four cases of anthrax In one case samples of bone fibre and meal were obtained, and the bone fibre yielded *B anthracis*

The bone-meal products were apparently Indian or Argentinian in origin, or a mixture of both

The strains isolated were all sensitive to penicillin, streptomycin, aureomycin, oxytetracycline, and erythromycin

We should like to thank Prof W J Tulloch for facilities and Dr A J H Tomlinson for giving us details of the yeastrel agar and permission to describe it, Dundee Sanitary Department for obtaining the bone fertiliser and for information concerning its origin, and Miss I M B Graham for technical assistance

REFERENCES

Davies, D G, Harvey, R W S (1955) *Lancet*, ii, 86
Jamieson, W M, Green, D M (1955) *ibid* i, 560
Lancet, 1957, i, 536
Pearce, T W, Powell, E O (1951) *J gen Microbiol* 5, 387

Addendum

We have seen within the past four weeks a further case of anthrax The patient was a seedsman aged 17 years with a typical lesion on the right forearm We have been able to demonstrate *B anthracis* from a sample of bone-meal handled by him, both by isolation in yeastrel agar and animal inoculation

In England Now

A Running Commentary by Peripatetic Correspondents

It is now some time since we became tired of writing scientific papers in which nobody was interested We felt that our psyche was cramped by these endless processions of *facts*, the limitless calvacade of introductions, techniques, results, discussions, and summaries, with their subsidiary acknowledgments, references, and illustrations It came to us that what we needed was an outlet for our personality, a larger canvas for our brush We determined to let our soul take wings We would write a book

Initially we detected a pervading apathy among the various publishers we attempted to favour with our custom "We recognise, of course," their letters began, "that the work you have been doing is of first-rate importance, but " Eventually, however, we succeeded in discovering a kindly firm who were basically sorry for us, and obtained an imposing-looking memorandum covered in red seals, in which we were hereinafter described as the author

The first proofs arrived heavily annotated in a fine Italianate *script by the translator* "*Cytoarchitectonics of the Umbilicus*," we had written baldly, "1 The Philosophical Background" This had now become "*Perp Titl 258 12 pt cap #d* $1^1/_2$ *pts R4 rule 24 ems Sub Perp 239 18 pt fig ital caps No Os*", and we were delighted to find ourselves so much in the technical swim We discoursed at length to our colleagues at morning tea on the relative advantages of Times bold face and Garamond in the production of scientific literature, and at lunchtime we went out and bought a spotted bow tie In the afternoon, however, we were mildly dashed to find, lurking among the pages, little interdepartmental publisher's messages They began innocently enough with "*Margin sheet pl*", but soon we began to detect a somewhat censorious, hectoring attitude "Charlie," read the second, "doubtful Latin p 15" Others were briefer, but not less to the point "C P," they said, marking our favourite purple passage, "*? constr Yrs* E R" *After a time relations between* C P and E R became slightly strained, and a brisk argument developed (over our prostrate body) on a grammatical point on p 127 But on the whole we saw no cause for serious alarm, and we relaxed into a happy daze of authorship

Our first intimation that all was not well came with the arrival of the first press copies, in a parcel bearing the bold-face label OF NO COMMERCIAL VALUE Since then we have seen all too clearly what they meant The reviewers have on the whole been tolerant, but they have made it clear that this has been a difficult task "Too long," they said, stifling a yawn "Too short," said others impatiently "Too detailed," said the clinical types, throwing down their pens to dash off to a subtotal viscerectomy "Too vague," said the back-room boys with scarcely concealed contempt "Too orthodox, too speculative, too turgid, too simple, unsuitable for students unsuitable for teachers, unsuitable for research workers, unsuitable "

The other day a distinguished guest was rummaging about in our library of *Penguins* when we heard our youngest child say to him in a sad meditative voice, "*My Daddy wrote a book* once It didn't sell "

* * *

Great progress is being made in medical knowledge and, for this, much credit must go to the epidemiologists who patiently ferret out fresh factors in the production of disease Thus in recent years we have learnt that the use of tobacco may well give us cancer of the bronchus or, at the best, chronic bronchitis, and, as if these were not enough, the smoker is now threatened with cancer of the bladder for his indulgence The comparatively virtuous glutton has been warned that his habits may lead him to a coronary infarct Resolute tipplers have shrugged aside fibrotic threats to the liver and neoplastic ones to the larynx only to find that the epidemiologists now promise them an increased risk of lung cancer because of prolonged residence in stuffy bars and drinking dens

It is not surprising if some of us are beginning to regard epidemiologists with considerable disfavour, for every fresh discovery of theirs only intensifies our chronic anxiety state But, to be fair, we must except the Pneumoconiosis Research Unit experts who cheered us up somewhat by reporting that inhalation of coal dust in moderate quantities would improve lung function. We are now wondering if addiction to coal-dust snuff could beneficially take the place of our present weaknesses

* * *

There is no doubt that convalescence broadens the scope of one's reading Never before have I had time to study those glossy circulars from the drug firms After carefully excluding those dangerous envelopes concealing samples of tablets I used to distribute all circulars, exactly, among the younger members of the family at breakfast (And woe betide me if one found more blotters than the other) But now the circulars come up to the bedroom with the breakfast tray and form part of my morning literary activity

The drug firms may not always quote the price of their product, but even the Hinchcliffe Committee would acknowledge that on occasion they are candid friends For instance we are told that one drug—with a reputation in tuberculosis but also useful in a variety of other diseases—has side-effects including constipation, difficulty in micturition, orthostatic hypotension, insomnia, impotence, headaches, and dizziness As if that were not enough, *pour encourager les autres*, there is also the chance of having muscle tremors, peripheral neuritis, and epileptiform attacks And finally the *coup-de-grâce*—jaundice.

There is a lot to be said, sometimes, for confining oneself to the disease with which one starts

* * *

Lincoln, in Massachusetts, U S A , is a little town close to the battlefields where the shot " heard round the world " was fired and English soldiers fought Englishmen " to keep the past upon its throne " When we moved to Lincoln as temporary summer residents, we were warned that even though we owed our allegiance to Her Majesty the Queen, we would have to take part in the town's annual Independence Day parade

At 10 A.M on a brilliant July 4 morning the parade moved off, led by the white-helmeted band of the National Guard and immediately followed by the town's oldest and newest fire-engines with sirens a-howling Then came a long line of symbolic floats carrying Lincolnites, old and young, in fancy dress We modestly brought up the rear in a Hillman Minx, its front decorated with a Union Jack and the boot surmounted by the Stars and Stripes and the Union Jack fluttering in unison In the hope of furthering Anglo-American relations, we had attached large placards bearing the jingles " 1775 but we're still alive " and " 1958, now we cooperate "

As we slowly drove along the route, the faces of the crowd looked puzzled and the applause was rather thin, so that our chances of winning any kind of prize seemed remote Then, at the last moment, just before we reached the judges' stand, we heard a loud voice " Guess they must be from the South " We treasure our third prize greatly

The echoes of that shot so many years ago are dying away

* * *

Science fiction has occasionally dealt with the psychiatric aspects of lunar voyages, and now that recent reports of plans to send rockets to the moon suggest that space travel may soon cross the line between fantasy and reality, is it not time to consider a rejuvenation of the term " lunacy " in psychiatric nomenclature? Perhaps a case could even be made for a lunatic syndrome, manifested by a morbid preoccupation with space travel, the presence of stellar phosphates in the urine, and, in the fully developed case, distortion of the features resulting in moonface Treatment of " moonshine " as it might come to be called colloquially, would probably be by administration of drugs such as 'Lunamil' or 'Lunatil' (one tablet three times a light-year) or by a process of conditioning by which the patient would be brought to earth

Letters to the Editor

THE DENTAL SERVICE

SIR,—Your leading article of June 21 discusses how dentists can be induced to give more of their time to the "priority classes"—children and expectant and nursing mothers But you do not mention the only way in which the profession in this country can provide adequate dental care for the whole population and at the same time recover its status I am speaking of the proper use of the right kind of ancillaries

Most dental students, on qualification, leave their hospital with high ideals and the ability to do, albeit slowly, almost everything a dental surgeon can do Our job can be very interesting, and the training we receive at hospital lays emphasis on its most interesting aspects—incidentally those which require intelligence and mental skill But what now happens when the young man gets into general dental practice? He finds immediately that the one part of National Health Service dentistry which is completely unpaid is the exercise of diagnostic ability and the use of the mental skills towards which his hospital training has been largely directed He finds that he is doing piecework and that his income for the rest of his career will be tied irrevocably to his output—regardless of its standard Thus committed for life to routine backbreaking work, paid at piecework rates, can he any longer be truly described as a professional man?

The alternative is not, as some of my colleagues think, higher pay for the same job—which is in any case unattainable—but a change in the pattern of our work No doctor would consider making surgical boots for his patients, or carrying out the many mechanical and semi-mechanical procedures necessary in treatment He has working for him a host of ancillaries—physiotherapists, radiographers, instrument-makers, nurses, and the like This is the way that dentistry also must go if it is to remain a profession Instead of deteriorating into hack workers, we dental surgeons must develop into a prescribing profession, in which we ourselves undertake only the more advanced procedures

There is in fact only one way to regain our proper position, and that is that we ourselves should plan and undertake, slowly and deliberately, the incorporation into dentistry of the right kind of ancillaries—not half-trained dentists, but fully trained technicians in one branch of purely technical dentistry These ancillaries would work under conditions laid down by the profession itself

Not only would this give a better service to the nation, and a better status to the profession, but it would also enable us to reverse the adverse pattern of earnings repeatedly pointed out in reports upon our profession, and enable dental surgeons, like physicians, still further to increase their skill and value to the community with experience

I am sure that ancillaries, properly used, are for the good of the profession, and it is up to us to see that those already legalised, and any that may be legalised in the future, are properly employed to increase both the efficiency and the status of dentistry in this country

London, W 1 J. H HOVELL

CHRONIC DISSECTING ANEURYSM OF THE AORTA

SIR,—The interesting report by Mr Eastcott and Dr. Sutton (July 12) calls for comment

(1) They speak of the diagnosis of dissecting aneurysm as "being rarely made" This is no longer true With the increasing recognition of the clinical signs of dissecting aneurysm it is becoming possible to diagnose the majority of cases during life (as their case was, by Professor Rosenheim) Of the last 34 cases seen at the Radcliffe Infirmary (24 confirmed at post-mortem, 5 having died at home and 5 being still alive) a correct clinical diagnosis was made in 21

(2) Radiological signs can be useful, even diagnostic[1] Widening of the aortic shadow as compared with previous films may, as Mr Eastcott and Dr Sutton suggest, be open to misinterpretation, but it is often a most helpful sign So is the appearance of calcification an abnormally long way in from the edge of the aortic knuckle

(3) The fact that a dissecting aneurysm extends from above to below the renal arteries does not necessarily, or even probably, mean that there is any interference with the blood-supply to the kidneys The dissection may not embrace the whole circumference of the aorta and it seldom extends into branch arteries, so that, although the dissection may surround the origin of the renal, or other, artery its lumen is not narrowed

(4) If the diagnosis of dissecting aneurysm has been made on clinical and radiological grounds one wonders whether it is wise to attempt to confirm it by arteriography The arteries of patients who have died from dissecting aneurysm are often friable, an arterial wall remote from the site of dissection can often be split into two layers by quite gentle rubbing Histological examination usually reveals marked cystic medial necrosis Although no reports have been published, so far as I know, of harm resulting from arteriography in cases of dissecting aneurysm it appears to be a risky procedure

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D A PYKE

INFLUENZAL ENCEPHALITIS

SIR,—We have read with much interest the accounts of encephalitis and neurological disorders associated with influenza by Dr Flewett and Dr Hoult, and Dr McConkey and Mr Daws, in your issue of July 5

May we draw the attention of pathologists to the importance of both virus studies and histological examination of the brain in all influenzal deaths, because it seems likely that some cases of influenzal encephalitis are missed at necropsy?

All are probably manifestations of the same pathological process, but further studies as suggested are still necessary to establish this Fatal cases of this important form of encephalitis should be correlated with the histological classification of encephalitis described by Greenfield[2] Complicated neuropathological techniques are not necessary for a diagnosis, but the brain should be fixed suspended in formol saline before sectioning The histological picture of hæmorrhagic leucoencephalitis is very characteristic The cortex and basal ganglia are spared, and the lesions in the white matter are of five chief types

(1) Necrosis of vessel walls including both small veins and arteries[3]

(2) Œdema of perivascular distribution with degenerative changes in the astrocytes

(3) A perivascular leucocytic exudation which becomes monocytic at a later stage

(4) Zones of perivascular demyelination containing excess microglial or histiocytic cells

(5) Perivascular ball or ring hæmorrhages

Meningeal infiltration by neutrophil leucocytes, lymphocytes, and histiocytes, which is often quite heavy, is also observed

These lesions are all readily recognisable in paraffin sections stained by routine hæmatoxylin and eosin They should be searched for in every case

Since 1953 we have seen 6 cases of encephalitis, of these, occurred during influenzal epidemics The 3 that came t necropsy all showed the histological picture we have described Greenfield[4] has obtained influenza virus A from the pulmonary lesions of a similar case but not from the brain W therefore agree with the view expressed in your annotatio that this type of encephalitis is the result of influenza W do not feel that such post-mortem findings can be explained by "severe anoxæmia and venous congestion" Also, w would like to point out that in most fatal cases of hæmorrhagi leucoencephalitis[4, 5, 6] the cerebrospinal fluid at some time ha shown a leucocyte count of several hundred per c mm and correspondingly increased protein This was our experienc also

Finally, we await with interest the report of the histo logical examination and classification of the brain in th first case described by Flewett and Hoult, from the lung of which influenza virus was isolated

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R A GOODBODY
R J McGILL

INTESTINAL ABSORPTION OF VITAMIN B_{12}

SIR,—Dr Heathcote and Dr Mooney (May 10) hav suggested that vitamin-B_{12}-peptides are absorbed from the small intestine by a process of diffusion across th intestinal wall It occurred to us that this hypothesis could be tested by examining the intestinal wall for th presence of such peptides

We have, therefore, fed radioactive vitamin B_{12} to four rat and, in each case, after 1 hour, have removed the portion o intestine which contained nearly all of the radioactivity taken up in this time The length of intestine removed was opened by a longitudinal cut, washed, and then homogenised in saline The homogenate was ultrafiltered through Visking membrane Had vitamin-B_{12}-peptide complexes been present, they would have passed into the ultrafiltrate and an appreciable amount of radioactivity would have occurred in this situation In actual fact the radioactivity in the ultrafiltrate was only a few per cent of the total uptake We can assume, therefore, that vitamin B_{12} in the process of absorption is bound in such a way as not to be ultrafilterable, and that it is not bound to a peptide The small amount of activity we found in the ultrafiltrate could be explained in terms of a dissociation equilibrium

Examination of the intestinal contents revealed a somewhat greater proportion of ultrafilterable vitamin B_{12} This, of course, may be the vitamin in the free state, but equally well could be a peptide complex

Our observations, therefore, lead us to conclude that the vitamin is not absorbed as a peptide complex They do not, however, exclude the concept that vitamin-B_{12}-protein complexes are broken down to vitamin-B_{12}-peptides in the intestine by a process perhaps involving intrinsic factor[7] and that the vitamin is then transferred to a protein acceptor in the intestinal wall Studies of vitamin-B_{12} binding by intrinsic factor preparations (Latner and Raine, unpublished observations) make it unlikely that binding to intrinsic factor itself is a preliminary to absorption

We should also like to point out that analysis in terms of the response at the 15th day[8] of the clinical results published by Dr Heathcote and Dr Mooney indicates that relatively small quantities of vitamin B_{12} were absorbed This too can be taken as evidence against the absorption by simple diffusion of unaltered vitamin-B_{12}-peptides, since the amounts of vitamin absorbed were very small fractions of the total amounts administered

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[1] Pyke, D A Post-Grad med J 1956, 32, 7
[2] Greenfield, J G Recent Advances in Clinical Pathology London, 1947
[3] Crawford, T J clin Path 1954, 7, 1
[4] Greenfield, J G Neuropathology London, 1958
[5] Adams, R D, Cammermeyer, J, Denny-Brown, D J Neuropathol 1949, 8, 1
[6] Greenfield, J G Brain, 1950, 73 141
[7] Latner, A L Lancet, 1958, i, 1077
[8] Campbell J A, McLaughlan, J M Vitamin B_{12} and Intrinsic Factor I Europäisches Symposion, Hamburg 1956, p 258 Edited by H G Heinrich. Stuttgart

We have, of course, yet to see the proof that Dr Heathcote and Dr Mooney were actually administering a vitamin-B_{12}-peptide and not a mixture of the free vitamin and a peptide In our opinion, the absorptions they obtained might well be expected from the administration in similar dosage of vitamin B_{12} alone, and control investigations are badly needed

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C GREEN
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DILUTION ANÆMIA

SIR,—The "physiological anæmia of pregnancy" is due to an increased plasma volume[1-4] Likewise, in chronic myelogenous leukæmia increased plasma-volumes have been found[5,6]

It is conceivable that low concentrations of hæmoglobin (Hb) in the peripheral blood may be explained as dilution effects in other states Such patients may have a normal amount of total body hæmoglobin (THb) (i e, 1·12 g per kg in males and 0·86 g per kg in females) and an increased total blood-volume

FOUR CASES ILLUSTRATING DILUTION ANÆMIA

Clinical diagnosis	Hb concentration	Calculated normal THb (g)	Actual THb in g (% of calculated normal)	Calculated normal blood-volume (ml)	Actual blood-volume in ml (% of calculated normal)	No of blood-transfusions given
Chronic nephritis with secondary anæmia	72%	339	350 (*106*)	2400	3500 (*146*)	>15
Postural hypotension with anæmia*	61%	592	556 (*94*)	3800	5900 (*155*)	>10
Myeloma	65%	405	449 (*111*)	2900	4800 (*165*)	23
"Hepato-megalic anæmia"	62%	625	591 (*95*)	4100	6200 (*152*)	>12

* This case has been reported previously[7-9]

Hb, THb, and blood-volume (estimated same day) in 4 patients Hb 100% for males = 15·4 g per 100 ml., for females 13·9 g THb determined by the alveolar carbon monoxide method[10], normal blood-volume = normal THb ÷ normal Hb concentration.

It is questionable whether it is possible or even desirable to increase the THb above the normal amount in such cases, in an effort to make the hæmoglobin concentration normal, by giving blood-transfusions, and it does not seem to be known whether adequate circulatory function or even the feeling of wellbeing is more dependent on the THb (i e, total red-cell volume) or on the hæmoglobin concentration. Until further information is available it seems reasonable to regard patients with normal THb as healthy from the point of view of anæmia

But cases of "dilution anæmia" may not be diagnosed as such and may be treated as having genuine anæmia Because the "anæmia" is refractory to other treatment, these patients are sometimes given numerous blood-transfusions (as well as parenteral iron and liver or vitamin B_{12}) over long periods of time (see accompanying table) The purpose of this letter is to draw attention to these states in the hope that blood-transfusions, which are probably unnecessary in simple hypervolæmia, and which are expensive and not without danger, may be avoided.

A more thorough examination of dilution anæmias is in preparation.

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1 Dieckmann W J Wegner, C R *Arch intern Med* 1918 53 596
2 Thomson K J, Hirschheimer A Gibson, J G Jr, Evans, W A. *Amer J Obstet Gynec* 1938, 36 48
3 Bethell F H, Gardiner, S H McKennon, F *Ann intern Med.* 1939, 13, 91
4 Gemzell, C. A., Robbe, H., Ström, G *Acta obstet gynec scand* 1957, 36 93
5 Forkner, C E *in* Leukemia and Allied Disorders New York, 1957
6 Berlin N I, Lawrence J H., Gartland, J *J Lab clin Med* 1950, 36, 435
7 Luft R., Sjögren, B *Nord Med* 1948, 40, 1764 (case 1)
8 Luft, R., Sjögren B *Acta endocr., Copenhagen* 1949, 2, 287 (case 4)
9 Luft R., von Euler, U S *J clin Invest* 1953 32, 1065 (case 1)
10 Sjöstrand T *Acta physiol scand* 1948, 16, 201, 211

SHOULD BIBLIOGRAPHIES GIVE TITLES OF PAPERS?

SIR,—The bibliography of American medical papers is much more valuable than that of British papers, because of the almost invariable American practice of giving titles Is it not time that we in this country adopted the American practice, and will not you, Sir, pioneer this advance?

The Middlesex Hospital,
London, W 1

DAVID H PATEY

*** We agree with Mr Patey that there are advantages in giving titles in references, but the extra space needed is, we think, too great to justify making this change in *The Lancet* Under our present system we use a weekly average of between one and two columns for references to original articles To include titles of papers would at least double this consumption To compensate for this, we should have to exclude an article of perhaps 1000–1200 words —ED L

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—Some of the questions raised in your annotation[1] are answered in work already published by us[2-10] This was recently summarised by us at the March meeting of the Comparative Medicine Section of the Royal Society of Medicine[10] To reiterate briefly the tendency to disc prolapse depends upon the intra-disc tension and the structural state of the annulus fibrosus and the nucleus pulposus

Increase of intra-disc tension possibly arises as a result of the "triggering" of a sequence of changes probably by an endocrine factor whereby, amongst other possible changes, depolymerisation of the polysaccharides of the nucleus leads to increased power of fluid absorption and thus increased fluid absorption with resultant rise in intra-disc pressure As the depolymerised molecules are removed there is a return to the status quo with relief of symptoms With each episode of symptoms, this process is repeated so that the total polysaccharide content is reduced, producing a degenerated, desiccated disc A stage will be ultimately reached whereby the concentration of the polysaccharide and power of fluid absorption are so reduced that prolapse cannot occur

Our intra-disc pressure measurements showed fluid absorption to produce the highest pressures in the 35–55 age-group, which parallels the incidence of disc prolapse Our X-ray crystallographic studies have shown that beyond the age of 40 the reduction of polysaccharide, though relative, is associated with precipitation of the collagen Such a process causes the incompressible gel structure of the nucleus pulposus to change to a fibrosed mass incapable of *uniform* transmission of stress This uneven dissipation of stress causes gradual attrition of the annulus With increasing age, precipitation of the collagen in the annulus results in decreased elasticity We

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1 *Lancet*, 1958, i, 1214
2 Naylor, A *Ann. R Coll Surg Engl* 1951, 9, 158
3 Naylor, A Smare, D L *Brit med J* 1953, ii, 975
4 Happey, F, McCrae T P, Naylor A Nature and Structure of Collagen, Faraday Society, London, 1953
5 Naylor, A, Happey, F McCrae, T P *Brit med J* 1954, ii, 570
6 Bush, H D, Horton, W G, Smare, D L., Naylor, A. *ibid* 1956, ii, 81
7 Happey, F, Horton, W G, McCrae, T P, Naylor, A *Nature, Lond.* 1955, 175, 1032
8 Hall, D A, Lloyd, P F, Happey, F, Horton, W G, Naylor, A. *ibid* 1957, 179 1078
9 Bernardi G, Happey, F, Naylor, A *ibid* 1957, 180, 1341
10 Naylor, A. *Proc. R Soc Med* (in the press)

suggest that nuclear herniation becomes less frequent in the older age-groups partly because of these changes in the gel structure and function of the nucleus and partly because there is insufficient polysaccharide to develop an adequate intra-disc pressure

Answering Mr Charnley's question,[11] we think this outline of our views parallels the concepts described in his letter

Physics Department,
Institute of Advanced Technology,
Bradford D L SMARE

Textile Department,
Institute of Advanced Technology,
Bradford F HAPPEY

Royal Infirmary,
Bradford 9 A NAYLOR

SIR,—At the 1954 autumn meeting of the British Orthopædic Association when Mr Charnley introduced into a discussion his postulate of the hyperhydration of the nucleus, he prefaced it with the remark that this was "a little fairy tale which he liked to tell to his students" I thought that this terminology indicated a becoming but proper modesty—becoming because the idea could clearly be the source (which is always necessarily imaginative) of a new and valuable concept, and proper because a proved factual basis for the concept was lacking So far as I know no experimental or other confirmation has since appeared, but the postulate seems none the less to be in some danger of being elevated into a thesis

When I first began my investigations into disc behaviour six years ago, Mr Charnley's original observations had already been published, and I expected that some evidence of a "super-saturation" phenomenon would indeed come to light This did not prove to be so, but I do not think that the divergence between the two views is as complete as is being implied Some confusion may well arise from the (to my mind) incorrect use of the word "desiccation" A man who has been sitting with rubber boots on and with his socks fully but exactly saturated with water, and who then stands up, is unlikely to complain that his feet are desiccated, although he may, if of a dispassionate turn of mind, concede that his socks have become drier An inefficiently functioning nucleus, similarly, becomes "drier" under load, but the significance of this lies in the excess of fluid which is thereby liberated Our rubber-booted, wet-socked citizen becomes conscious of water-exchange on weight-bearing, our annulus in like manner suffers from the repeated appearance of abnormally large volumes of suddenly "unbound" tissue fluid Furthermore as the annulus loses its elasticity and the nucleus accordingly becomes almost completely unstressed with recumbency, the gel has to work on that part of its imbibition pressure-saturation curve where (the curve being exponential) a given increment in load is accompanied by the maximum change in saturation And all this in a cavity with two rigid walls and a strictly limited rate of fluid diffusion If these phenomena are inadequate to explain the eventual rupture of an already weakened annulus, then perhaps I should, in the best Scots manner, take to studying imbibition in another form

Mr Charnley cites the difficulty of explaining on this basis the attack of "lumbago" that lasts as long as three weeks I cannot say that I find such long-lived symptoms and signs common unless in patients who then or subsequently produce root signs But is there any reason for the pain's not lasting as long if the ruptured fibres of annulus happen to include a sizeable nerve-fibre? Or if a cartilage end-plate is damaged? Or if the pain threshold is low? Or is there any proof that the pathology is in fact then in the disc? Can this picture not appear with facetal joint strains, interspinous ligament tears, minor congenital abnormalities of dura or vertebræ, with the vicious circle of muscle spasm—pain—muscle spasm, or even perhaps—since fancy may apparently sometimes obtrude in discussions of fact—the incarceration of dephlogisticated air (notoriously obdurate of absorption as I understand) in a dural pocket?

The fact is, of course, that none of us can answer even the beginnings of all the questions in disc pathology We are entering a field of what could optimistically be described as new knowledge, but which is more realistically seen as fundamental ignorance The basic chemistry and the metabolism of the polysaccharides are closely involved, and are so far largely unknown It is clearly possible that Mr Charnley's postulate will subsequently find confirmation, and that the physical abnormalities I have found are of less significance than I think, or capable of different interpretation But in so difficult a field would we not do well, in the meantime, to avoid discussions based on conjecture, or on intuition, or on highly subjective considerations such as the character of the pain produced, and concern ourselves with such facts as have been demonstrated? There is already a reasonable basis of pathological physics to work on and a great mass of accurately observed anatomical change The next step should surely be to enlarge or to revise that basis by physical experiment or to investigate its chemical, and eventually its metabolic, background

Royal Infirmary, Aberdeen NEIL G C HENDRY

RECORDS OF IMMUNISATION

SIR,—I have read with interest the correspondence which started with Dr Randall's letter of May 3

In the Southern Gas Board we decided, in consultation with Dr H J Parish, of the Wellcome Research Laboratories, to offer active immunisation with tetanus toxoid on a voluntary basis to all men employed in our mains and service laying gangs

The records of the inoculations are entered on the cards provided by Messrs Burroughs Wellcome, and on completion of the third injection the card is given to the patient with instructions to carry it on him and, should he at any time be taken to hospital, to present the card to the doctor who treats him

There is on these cards plenty of room for the inclusion of details of any other immunising injections which the patient may receive

Medical Department,
Southern Gas Board, Southampton M B CARSON

TREATMENT OF NEPHROTIC NEPHRITIS WITH CHLOROQUINE

SIR,—We have observed a favourable effect of chloroquine on the nephritis component of systemic lupus erythematosus [1] According to Mellors [2] there is a similarity in the pathogenesis of the nephritis of lupus and that of the nephrotic type of chronic nephritis

Accordingly we have treated in this hospital three patients with the nephrotic type of chronic nephritis by bed rest, low-sodium diet, and chloroquine diphosphate in doses ranging from 0 75 g to 1 g daily for 2 to 4 months In each case the nephrotic syndrome has disappeared, with suppression of œdema, increased diuresis, and subsidence of hæmaturia Proteinuria fell from 3 2 g per litre to 0 25 g in the first patient, from 25 6 g to 0 20 g in the second, and from 34 7 g to 0 20 g in the third, during a period of 30 days α_2-globulin fraction and serum-cholesterol became normal and the total serum-protein level rose significantly

A control group of 26 patients with the nephrotic type of chronic nephritis were observed during 1 month in the same hospital, and were treated with bed rest and low-sodium intake In this group the variations in proteinuria, serum-cholesterol, and serum-protein were studied and their standard deviation determined The proteinuria varied from 6 49 g per litre to 7 58 g during the month The probability that the good results in the chloroquine group were due to chance is less than 1 in 10,000

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[11] Charnley, J *Lancet*, 1958, i, 1277

[1] Plaza de los Reyes, M, Campos, R., Orozco, R, Matus, I, Berrios, R *Rev Med Chile*, 1958 (in the press)

[2] Mellors, R. C., Ortega, L G, Holman, H R *J exp Med* 1957, 106, 191

Clinical and laboratory control for 2, 3, and 4 months respectively continued to show a satisfactory recovery No side-effects were observed.

Despite the small number of cases, we feel these results are worth recording

Aguirre Hospital,
University of Chile, Santiago
M PLAZA DE LOS REYES

INTESTINAL ANGINA

SIR,—Your leading article of June 7 is very informative and timely As former professor of internal medicine at the University of Vienna I feel I should draw attention to the fact that the late Prof Norbert Ortner was quite familiar with this disease and first described it in all its details long before it was "rediscovered" as a clinical entity One thing that prevented Ortner's syndrome from being generally recognised was probably his term "dyspragia intermittens angiosclerotica intestinalis" In my *Differential Diagnosis of Internal Diseases*[1] the clinical picture and its history has been briefly discussed

Los Angeles
JULIUS BAUER

RADIATION HAZARD IN ANTENATAL RADIOGRAPHY

SIR,—In the investigation of the hazards in diagnostic radiology the recent approach has been to study the histories of the children with leukæmia and other malignant conditions and in retrospect assess the exposure to radiation The series recorded here consists of all patients referred during the year *1948* for pelvimetry, and although the number is relatively small I feel the results are none the less significant

The year 1948 has been chosen to give a reasonable period for any harmful effect to become apparent in the children, and pelvimetry examinations have been selected in view of the high radiation dose involved. Information regarding the present wellbeing of the children has been obtained by kind cooperation of the health visitors, without whose help the follow-up would not have been possible, in view of the large population shift within and from Glasgow during recent years

The investigation covers 148 patients, all referred for pelvimetry to exclude pelvic contraction The average number of films per patient is 3, which is three times the present figure for the examination In 1 case, straight films for maturity and viability were taken, and 7 films were used, the largest single figure As the X-ray unit in use in 1948 is no longer available it is not possible to assess the dose-rates received The children of 104 of the 148 patients are alive and well, 21 are deceased due to causes listed below, and 23 have not been traced, some having emigrated Of the deceased there has been no report of leukæmia or other malignant condition

	No of deaths
Stillbirth	7
Pneumonia	4
Gastroenteritis	2
Accidents	2
Congenital abnormality	3
Unknown	1
Miscarriage	2

Since these children were submitted to a relatively high radiation dose compared with the present technique it is reassuring to know that as far as can be ascertained no case of leukæmia has been reported

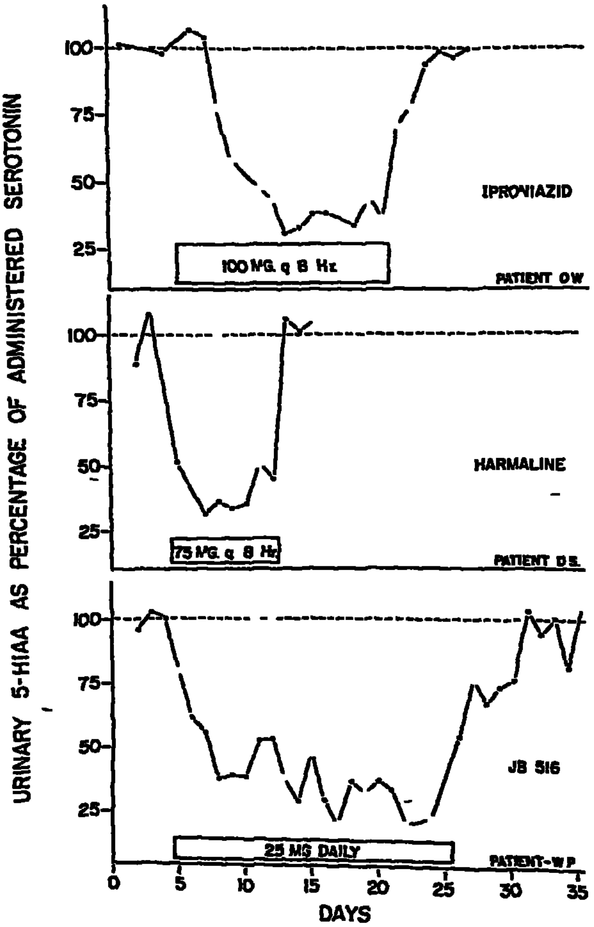
I should like to thank Dr R McG C Crawford, consultant radiologist, for suggesting this investigation and for helpful advice The follow-up of the children's health would have been impossible without the active cooperation of Dr N I Wattie, principal medical officer for maternity and child welfare, and her health visitors

Southern General Hospital,
Glasgow
W H DEMPSTER

A SIMPLE METHOD FOR THE MEASUREMENT OF MONOAMINE-OXIDASE INHIBITION IN MAN

SIR,—There is currently much interest in the therapeutic potential of drugs which have been shown in animals to inhibit the enzyme, monoamine oxidase (M A O) The best-known of these agents, isopropyl-isonicotinyl hydrazine (iproniazid, 'Marsilid'), is being used in psychiatry in depressed patients, as well as in the treatment of two cardiovascular disorders, hypertension and angina pectoris[1] A pertinent question is whether these agents do inhibit M A O to a significant extent in man and, if so, whether the therapeutic effects are the results of the M A O inhibition To help answer these questions we have devised a simple test based on the conversion of orally administered serotonin to 5-hydroxyindolacetic acid (5-H I A A), the end-product of M.A O activity[2]

Following oral administration of an arbitrary dose of 20 mg of 5-hydroxytryptamine (serotonin), urine is collected for an 8-hour period and assayed for 5-H I A A[2] Repetition of this procedure on several successive days establishes a control range of conversion to 5-H I A A for a given patient, usually between 18 and 22 mg per 8 hours This procedure is con-



Effect of M.A.O inhibitors on conversion of serotonin to 5-H.I.A.A. in man tinued during the administration of a presumed M A O inhibitor

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[1] Bauer, J Differential Diagnosis of Internal Diseases New York, 1955

[1] Symposium on Iproniazid *J clin exp Psychopathol* suppl, 1958, 19

[2] Udenfriend, S, Titus, E. O, Weissbach, H *J biol Chem* 1955, 216, 499

Although infusions of serotonin are poorly tolerated, the oral administration of serotonin should be of no concern since a common food item, the banana, contains considerable amounts of it [3] We have administered as much as 50 mg of serotonin orally to patients without any observable effects, even in the presence of M A O inhibitors During these studies the only effect observed was orthostatic hypotension, attributable to the M A O inhibitors themselves

The results obtained with three drugs are presented for illustrative purposes (see accompanying figure) They were administered on a regular schedule, stipulating only that a dose be given 2 hours preceding the administration of serotonin each day It is apparent that all three drugs markedly reduced the conversion of serotonin to 5-H I A A Iproniazid and (1-methyl-2 phenyl)-ethyl hydrazine hydrochloride (JB-516)* are examples of long-acting M A O inhibitors Harmaline, a harmala alkaloid recently shown to be a potent inhibitor of M A O in animals,[4] is an example of a short-acting inhibitor [5]

The reduction in the percentage of conversion of serotonin to 5-H I A A indicates that these agents do inhibit M A O in man, and that the inhibition may be quite marked From previous studies with animals it is known that all three drugs reach the target enzyme throughout the body [1,5,6] Diminution of 5-H I A A production by this test may therefore be taken as representative of an overall inhibition of M A O, although it presumably measures only the inhibition occurring in the gastrointestinal tract and probably in the liver

There is a widespread flurry of activity to uncover new compounds which will possess such inhibitory effects with a minimum of toxicity For these reasons we have devised this simple test, applicable to man, realising that further refinements in its application will be forthcoming and hoping that this type of procedure will place M A O-inhibition therapy on a rational basis It will also be interesting to determine whether there are disease states in which M A O activity is impaired

Section of Experimental Therapeutics
and Laboratory of Clinical Biochemistry,
National Heart Institute,
National Institutes of Health,
Bethesda, Maryland

ALBERT SJOERDSMA
LOUIS GILLESPIE, JR
SIDNEY UDENFRIEND

CLEAN BLANKETS

SIR,—Because the sterilisation of woollen blankets, while preserving their natural properties, appeared to be impossible, attempts were made to devise a substitute In view of the recent publicity in the Press this letter is written to inform your readers that a boilable bedcover with all the social properties of the conventional blanket is under trial It has been found to be warm and comfortable, is easy to launder, handles well, is durable, and is reasonably cheap Work is still in progress testing the effects of bactericidal chemicals and their carry-over after washing It would be premature at this stage to give further details, for the blankets are not yet available in commercial quantities

Nuffield Department of Surgery,
University of Oxford

J S CALNAN

SIR,—Your leader of May 17 draws attention to the part played by woollen blankets in spreading infection in hospitals It is now possible to obtain cotton blankets that give the same thermal insulation as wool at less weight and less expense They can be sterilised and laundered by the methods used for other cotton articles

This type of material was developed at the Shirley Institute, and was the subject of experiments on cross infection in hospitals reported by Blowers, Potter, and Wallace [1]

British Cotton Industry Research Association,
Shirley Institute, Didsbury,
Manchester

H M TAYLOR

THE MEDICAL DIRECTORY

The Editor of *The Medical Directory* writes

"The annual schedule, upon the return of which the accuracy of *The Medical Directory* depends, has recently been posted to all traceable members of the medical profession, and its speedy return would be appreciated

"A number of schedules, sent to a doctor's last known address, have been returned through the post office marked 'Gone Away' Although in such cases every effort is made to find a new address, I should like to remind practitioners that if these efforts are not successful before the book goes to press, the names in question will be omitted from the next edition

"Any doctor who has not received the annual schedule, or who has mislaid it and would like a duplicate, is requested to communicate as soon as possible with The Editor, The Medical Directory, 104, Gloucester Place, London, W 1 The full name and year of qualification of the doctor should be sent for identification, please"

Parliament

Prevalence of Bronchitis

ON July 9, on the adjournment, the Rev LLWELYN WILLIAMS drew attention to the fact that Britain has the worst record in the world for bronchitis The death-rate was four times as high as that in the Ruhr or industrial Belgium, and about twenty times as high as that in the Scandinavian countries In nearly all other countries the death-rate had fallen since the end of the war, but in Britain the position was substantially the same as in 1940 despite the introduction of new and powerful drugs People often waxed indignant at the number of days lost through strikes, yet in 1956 industrial stoppages were responsible for the loss of 2 million working days while bronchitis was responsible for the loss of 25 million

QUESTION TIME

Security Precautions at Broadmoor

Mr MARCUS LIPTON asked the Minister of Health what action he would take to improve security precautions at Broadmoor —Mr WALKER-SMITH replied The Board of Control has decided to hold an inquiry into the recent incident at Broadmoor Institution, and I must await its report Mr LIPTON Will this inquiry be a full inquiry, in view of the widespread public misgivings caused by the recent escape? For example, will the inquiry take note of the unanimous view of the 230 male nurses in London, employed at Broadmoor, who have made urgent representations to the Minister that, from the security point of view, the Home Office should have some say in this matter?

Mr WALKER-SMITH This will be a full inquiry in the sense that it will inquire into all matters which are relevant and into which it is constitutionally proper for the Board of Control to inquire —Mr A R HURD Will this be an independent inquiry such as the Scott Henderson inquiry?—Mr WALKER-SMITH This will not be an independent inquiry in the sense of the Scott Henderson Committee I have already said that this is an inquiry by the Board of Control It is an inquiry into this specific incident which is the first serious escape since the publication of the Scott Henderson findings in 1952 The procedures were reviewed by the Scott Henderson Committee This is obviously a more narrow approach

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* Synthesised and supplied by Lakeside Laboratories, Milwaukee, Wisconsin

[3] Waalkes, T P, Sjoerdsma A, Creveling, C R, Weissbach, H, Udenfriend, S *Science*, 1958 127, 648

[4] Freter K, Weissbach, H, Redfield, B, Udenfriend, S, Witkop, B *J Amer chem Soc* 1958, 80, 983

[5] Udenfriend, S, Witkop B, Redfield, B, Weissbach, H To be published

[6] Spector, S, Prockop, D, Shore, P A Brodie, B B *Science*, 1958, 127, 704

[1] *Lancet*, 1957, i, 629

Mr R. T. PAGET Will the Minister bear in mind the remarkable achievements in curing people by Broadmoor and not be panicked by this sort of thing into making medical treatment in Broadmoor impossible?—Mr WALKER-SMITH I have in mind these considerations as well as the conditions of security.

Shortage of Nurses

Mr P. C. GOODHART asked the Minister how many beds in mental-deficiency units were out of commission in the South-East Metropolitan Regional Hospital Board area because of shortage of nursing staff. Mr WALKER-SMITH replied 230.

Mr GOODHART Is the Minister aware that the number of beds standing empty because of shortage of staff is nearly equal to the number of mental patients awaiting entrance to these units in this area?

Royal Commission on Remuneration

Mr KENNETH ROBINSON asked the Minister whether the Royal Commission on Doctors' and Dentists' Remuneration had finished taking evidence, and when he expected to receive its report. Mr WALKER-SMITH replied The process of taking evidence and collecting necessary information will not be completed for some months, and, while the Commission intends to submit its report as quickly as possible thereafter, it does not expect to be able to do so until next year.

W.H.O. Malaria Fund

Mr ARTHUR BLENKINSOP asked the Minister whether he would make a contribution to the World Health Organisation's malaria fund.—Mr RICHARD THOMPSON, the parliamentary secretary to the Ministry, replied It is not possible in present circumstances to supplement the contributions which we make to the regular budget of the World Health Organisation. We are in any case already making substantial contributions in this field. Mr BLENKINSOP Before the parliamentary secretary turns this down altogether, may I ask him to ask the Minister and the Chancellor of the Exchequer to look at the implications of this matter again, in view of the very high scientific advice which is available that this is a most urgent world problem and that we stand to gain from its solution as well as everybody else in the world?—Mr THOMPSON Yes, but we are opposed to the creation of special funds financed by voluntary contributions for organisations which are normally financed by compulsory assessment on member States.

Health Centres

Since the start of the National Health Service, local health authorities have established 9 health centres. 3 are under construction, and another will be started this year. 9 other schemes have been proposed, and 3 at least of these are likely to be started in 1959-60.

Mental Health Services

In the last financial year about 11½% of the total cost (about £585 million) of the National Health Service is identifiable as having been spent on mental health services. This includes 11% by hospitals (about 19¼% of their expenditure) and ½% by local health authorities (about 5½% of their expenditure). Certain administrative expenses of hospital authorities, which cannot readily be identified with individual hospitals, and the cost of beds for mental illness in acute hospitals, which cannot be separately ascertained, are not included. Similarly local health authorities incur some additional expenditure on mental health which is not separable from that on their other services.

Carbromal and Bromvaletone

The Poisons Board, at its meeting on June 18, decided that the evidence before it was insufficient to warrant any change in its recommendation of 1955 that preparations containing carbromal, or carbromal and bromvaletone, should not be controlled under the Poisons Act. The Home Secretary has accepted this recommendation. The Minister of Health proposes, however, at the suggestion of the Board, to invite the committee on drug addiction, recently set up under the chairmanship of Sir Russell Brain, to examine further the risks attending the abuse of such preparations.

Obituary

ISIDOR CLINTON RUBIN

M.D. Columbia

SOME of the finest ambassadors have no ambassadorial rank, and Dr Rubin, the distinguished American gynæcologist, who died in London on July 10, was a member of this small band of world citizens, for by his vision, warm sympathy, gentle culture, and manner of living he denied the artificial bounds of race, colour, and political dogma.

He studied medicine in New York and became an M.D. of Columbia University in 1905. He worked at Mount Sinai Hospital from 1905 to 1909 with Dr H. N. Vineberg, who advised him in 1909 to go to Vienna for further study. There Rubin came under the influence of Professor Schottlander, pathologist to the University Frauenklinik, who introduced him to laboratory methods of scientific work and helped him to prepare his first papers. In 1910, on his return to the United States, Rubin was appointed gynæcologist at the Beth Israel Hospital, and in 1929 he became director of the gynæcological service there. From 1937 to 1947 he was clinical professor of gynæcology at Columbia University, and from 1948 clinical professor of obstetrics and gynæcology at New York University.

He was honoured in many countries. In 1955 he was made an officer of the French Legion of Honour, and the Royal College of Obstetricians and Gynæcologists of Great Britain made him an honorary fellow in 1957. He was a familiar figure at congresses all over the world, and he was a welcome visitor to the last British Congress of Obstetrics and Gynæcology, held at Oxford in 1955.

Rubin will perhaps be best remembered for his work on tubal insufflation, of which J. A. S. writes:

It was in 1914 while he was working in the laboratory of Wertheim at Vienna that Dr Rubin first became interested in the demonstration of the uterus and tubes by radiological methods. He injected 'Collargol' into the postmortem human uterus and into the uterus of living rabbits. He was quick to realise the possibility of diagnosing submucous fibroids by this technique and he saw that with this new method it would be possible to demonstrate tubal patency in the living by the use of radio-opaque solutions. Collargol was not adopted in practice because of toxic side-effects, but later, when 'Lipiodol' was developed, the technique of hysterography and salpingography became a routine procedure in fertility testing. Rubin then realised the possibility of using gas to demonstrate tubal patency, and in 1919 at Mount Sinai Hospital in New York he performed his first uterotubal insufflation. His many subsequent papers chronicle the developments and improvements of this technique, the carefully laid-down criteria for its safe performance, and analyse critically the results achieved. His interest in this problem was much deeper than many have appreciated, for he was not engaged in merely demonstrating tubal patency. He was interested above all in function. His work threw much light on tubal function from anatomical, physiological, pharmacological, and clinical points of view. He demonstrated the relation between tubal function and the hormonal factors of the menstrual cycle. He tested and recorded the pharmacodynamic influence of various drugs on the uterus and tubes. However encouraging the results, Rubin was always searching for something better, and until the day of his death he was still investigating the ideal radio-opaque medium for use in radiological investigations of the genital tract.

His published papers show the breadth of his interest. Like Bonney, he was a firm believer in conservative techniques when these could be employed without hazard to the patient. He was an advocate of myomectomy instead of hysterectomy during the childbearing years He was keenly interested in the problems of pelvic pain, dysfunction due to autonomic factors, and the influence of hormones on the genital tract, and in the importance of gynæcological pathology He has been justly described as a prolific writer More important, however, is the fact that his contributions were all examples of clear thought and concise expression His collected papers, from 1910 to 1954, were published privately in 1954, and those who have read the collection will have been impressed by the generous tributes paid to him in the three forewords by distinguished colleagues from three different countries Dr Emil Novak from Johns Hopkins, Dr Axel Westman from Stockholm, and Dr Bernard Zondek from Israel, all wrote simply and sincerely of his high scientific integrity, of his modesty, of his profound culture and noble character, and of those social graces which made him such a delightful companion

Dr, Rubin was an outstanding surgeon and a great man much beloved We mourn his passing but are grateful for his life and work

CYRIL JOHN MORGAN

M B , B Sc Wales, D P M

Dr Morgan, consultant psychiatrist and medical superintendent of Morgannwg Hospital, Bridgend, Glamorgan, died on June 26 at the age of 42

He was born at Penydarren, Merthyr Tydfil, Glamorgan, and he was educated at Cyfarthfa Grammar School, Merthyr, and at the Welsh National School of Medicine in Cardiff, where he graduated B SC in 1936 and M B in 1939 After holding a resident appointment at Pontypool Hospital he joined the R A M C , and served as a psychiatrist in this country and in West Africa until he was demobilised in 1945 The same year he joined the staff of the Rainhill Hospital, Liverpool, where he became senior medical officer He took the D P M in 1947, and in 1949 he was appointed deputy medical superintendent at Morgannwg Hospital, Bridgend He became medical superintendent four years ago He leaves a widow and three young sons

M D A writes.

Cyril Morgan was a truly dynamic personality, and he will ever live in the memory of all who knew him for his innate kindliness, his ever ready help, his seemingly tireless energy, and his infectious enthusiasm He was a brilliant and stimulating conversationalist, and had an exceedingly wide range of interests

ANDREW MEARNS FRASER

M D Edin , D P H

Dr Mearns Fraser, who was medical officer of health for Portsmouth from 1896 to 1934, died on July 8 in the Royal Portsmouth Hospital at the age of 90 To the older generation of public-health doctors his name will bring back memories of a man of outstanding ability and great personal charm

He was born at Reading and educated at the City of London School and at the University of Edinburgh, where he graduated M B in 1893 Two years later he took the D P H and joined the staff of the Essex County Council as assistant M O H , and he held this post until he moved to Portsmouth in 1896

H C M W writes

During the expansion of the health services in the early part of the century Mearns Fraser was one of the pioneers in the development of the tuberculosis service, and he established one of the first of the tuberculosis dispensaries, which was known in Portsmouth as the "tuberculin dispensary" After the 1914–18 war he took an active part in the campaign to check the dissemination of venereal diseases At that time he met with a great deal of opposition in his advocacy of the use of potassium permanganate as a prophylactic because it was thought that this would lead to promiscuity Apart from organising efficient local clinics and other services he supported many national bodies associated with preventive medicine He was a member of the council of the Society of Medical Officers of Health, of the departmental committee set up by the Local Government Board in 1912 on the future national policy to combat tuberculosis, and of the departmental cancer committee

When he retired in 1934 the regard and affection in which he was held by his staff and the people of Portsmouth was shown by the many tributes and presentations made to him. He retired to Hayling Island close to the golf course, so that he might enjoy to the full his well-earned years of retirement in a place that offered all the facilities for his favourite recreation. His many friends were delighted that he was still playing up to two to three years ago

Dr Mearns Fraser leaves a widow and two daughters

Sir ARNOLD STOTT

H S C S , who with Stott was one of a trio who worked and played together from their last years at Cambridge till the end of their house-appointments at Barts, writes

Arnold was really very consistent once it was grasped that his true period was the late 18th or early 19th century, when society was still essentially aristocratic Medicine he made his chief and therefore very successful hobby, but he might have been equally outstanding in the cotton world of Manchester, and probably ended his career as lord lieutenant of the county He was the most generous and kindhearted of men, but simple little remarks, really thinking aloud and uttered in his cool deliberate voice, which were the delight of his friends, sometimes had a devastating effect on those who only knew him slightly At our last meeting at the Fountain Club shortly before his retirement, which we were discussing, he remarked suddenly, " One thing really distresses me People so often seem afraid of me Why is it ?" and it was a great shock to think that perhaps with his seniority that could be possible though well-nigh incredible

By his transfer from Barts to Westminster the latter hospital had the great good fortune to acquire one of the last of the " vintage " physicians

Appointments

CAIRNS, J G , M B Glasg , D P H M O H , Halifax

CAPSTICK, A L , M B , B SC Wales, D P M assistant psychiatrist (S H M O), Whitchurch Hospital, near Cardiff

DONOVAN, J F , M R C S , D P M medical superintendent, St Lawrence's Hospital, Bodmin, Cornwall

GARFIT CLOWES, LOUISE M E , M B Belf , D P H assistant M O , Surrey

LATHAM, ALICE, M B , B SC Wales, D OBST , D C H assistant M O , Surrey

ROBERTS, T E , M B Lond , D OBST , D P H deputy M O H , High Wycombe and Marlow, and assistant M O and school M O , Buckinghamshire

SPARROW, OLIVE M , M D Lond assistant M O , Haltemprice, near Hull

SPENCER, S J G , D M Oxon , D P M consultant psychiatrist, Digby Wonford Hospital, Exeter

ZALIN, HAROLD, M B Lpool, F R C S E , D L O part-time consultant E N T surgeon, Walton Hospital, Liverpool

The Hospital for Sick Children, Great Ormond Street, London:

CORLETT, KEITHA, M B , N Z , M R C P , D C H house physician

LEADER, LESLEY P , M B , B SC Lond , M R C P house physician

MUNRO, A I , M B Lond house surgeon

WESTON, H J , M B N Z , M R C P , D C H resident assistant physician

WILSON, P E , L R C P I , D P H assistant medical registrar

Newcastle Regional Hospital Board:

DAYAN, ELIA, M B Cairo, F R C S senior casualty officer, South Shields group of hospitals

DUTTON, J E M , M B Durh , F R C S consultant neurosurgeon, Sunderland hospital group and regional neurosurgical service

HENDERSON, C B , M D Durh , M R C P consultant cardiologist, regional cardiovascular unit, Newcastle General Hospital, and regional thoracic surgery centre, Shotley Bridge General Hospital

ISMAY, GEOFFREY, M D Durh , M R C P consultant general physician, south west Durham and Durham hospital groups

MARSHALL, MERLIN, M B Cantab F F A R C S consultant anæsthetist, Newcastle upon Tyne hospital group

NEAL, F E , M B Sheff , D M R T assistant radiotherapist (S H M O), regional radiotherapy service

WELCH, R G , M D Lond , M R C P consultant pædiatrician, Hartlepools and Tees side hospital groups

Notes and News

WORK OF THE KING'S FUND

At the sixty-first annual meeting of King Edward's Hospital Fund for London on July 10, the Duke of Gloucester, the president, said that the Fund's grants had provided improvements of many kinds Very many hospitals showed the results of the Fund's grants to provide better living conditions for the nurses To build a recreation hall was often too large an item to be met by any other means than a grant from the King's Fund, and the Fund had now given a number of such halls, as well as making many improvements in nurses' homes At present there was a great need in some hospitals for better arrangements for the increasing number of staff who were non-resident, and the Fund had made grants to provide changing-rooms and sitting-rooms for them The Duke referred to the great difference that might be made to the quality of the future hospital service by various training schemes financed by the Fund The work of the three staff colleges—for ward sisters, for hospital administrators, and for future matrons—as well as the School of Hospital Catering, had led to results which were no less real

Lord Ashburton, the treasurer, moving the adoption of the accounts, said that last year for the first time the Fund's income had exceeded £400,000 This included a further instalment of £50,000 from the Nuffield Trust for the Special Areas In all the King's Fund had distributed more than £16 million to the hospitals of London, and still held a capital of over £7 million

INSTITUTE OF MEDICAL LABORATORY TECHNOLOGY

For the fourth time in fifteen years, this institute has moved to larger premises because of the growth in its membership and commitments Its new headquarters at 74, New Cavendish Street, Harley Street, London, W 1, were acquired at the end of last year and were occupied in May At the house-warming on July 2, Prof E T C Spooner, the president, received many pathologists who are honorary fellows of the institute, in addition to several past and present officers and others closely associated with its work

The voluntary Association which was the forerunner of the present institute took some thirty years to reach a total of 1000 members, which was its strength when the institute was incorporated in 1942 The increase to nearly 7000 members today is an indication of the expansion of the pathology services

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University of Oxford

On June 26 the following degrees were conferred

D M—S J G Spencer
B M—Colin Bell (in absentia)

University of Cambridge

On June 25 the degree of B CHIR was conferred on the following

A R Adamson, D I Atkinson, J S Bailey, P J Ball, J E Banatvala, Michael Barry, J R Bartlett, Anne C Bayley, P J Beale, D L Belcher, P M J Bennett, D A Birkett John Blake, S S Bleehen, Shirley A Bolt, P D G Briggs G C Brill M H Brooke, E P Brooks, F T Brough, J M Brown, Margaret U Bullen, H P R Bury, W D Callum, I G Carnegie Brown C J Carr, I R Carr, Ian Chippendale, P W Clements, R D Cohen M J Corrigan, A D Crawford, J R B Currie, Derek Davies G M Davies, M H Davies, Nerys Davies, Clare E Durrant, A J Earl, J S Elkington, R M M Fordham, P B Garland, T W Gibson J E Godrich, R J M Gold R B Harcourt, J D Hardcastle, N A Harker, D C Harvey, W R Heaton, John Hedley-Whyte, A A Hooper, J R Holye, Yvonne P Humphreys I D Hunter-Craig, R K Jackson J D Jeremiah, M L Johnson, R H Johnson, Audrey E Kermode, R A Kipping, C G Koo, J R Langmaid, N K Leiper, P O Liebling, R M Lodge J W Mack R J Mitchell Tony Moreton H G Morgan, M G E Morgan, Brian Newbigin, N W Oakley, M J O Shea, J D Owen, J S Paddle, P W S Patton, E N Payne, P V Pigott, G E T Raine, M J Ramsden M J Raphael, R J Read, Allan Reynolds J C Rice, A B Richards, Brian Richards, D J Richards Valautham Rudralingam, Heather M Rumsey, Nanju Sankarayya, D C L Savage W G Shakespeare J M Shepherd, Margaret R Skelton, A C Smith T A L Smith, J W Soper, J C Southam, J E Stark, J M Stephenson S O Suite, A J Taylor, M E Tuck, H B Valman Mary Walker, Daphne M Ward D B Watkin, John Weston W F Whimster, D M Whiteford, Alan Whitworth, D H Whyte-Venables, M E Wilson, F G de L Wright, Richard Yeo

University of London

At recent examinations the following were successful

D T M & H—A H Nasr
D P H—J A R Anson, A J Barwood, Anand Bhoomkar, G Castle, Elizabeth P Cloake, W G Cooke, Elizabeth J Coulter, W E Crocker, Evelyn C Cummings, L A C-R C da Motta, W R Davies, Margaret Duncan, Bernard Gampel, A K Gupta, D F Hadman, Thomas Hall, D R Haupt, A J Hibell, E G Larson, Huan-Ying Li, P G W A Lommerse, Christopher Lydon, R W McCollum, W H McDonald, H F McElligott, W R McKibben, J A McKinnon, C J H Mann, Ann B Marples, Machupe Mphahlele, Rudolf Neumann, Satya Ranjan Ray, T H Redfern, J H Sewart, Henry Shore, E R Simpson, J J Slome, L S Sodhy, R H Strudwick, David Sturman, S V Tamhane, G S Udall, J de M Vink, M W L White, R E Woolley, J R R Wray

University of Birmingham

On July 4 Prof A Lacassagne, of the Pasteur Institute in Paris, opened clinical research laboratories at the Medical School The laboratories, which have cost £50,000, were provided by the Birmingham branch of the British Empire Cancer Campaign

They are situated on the site reserved for clinical research near the Queen Elizabeth Hospital and the Medical School at Edgbaston The laboratories will permit all cancer research in Birmingham to be centred in one place Dr John Orr, professor of pathology in the university and director of cancer research, has been closely concerned with the project After Professor Lacassagne had declared the laboratories open, Prof L Severi, of the University of Perugia, unveiled a plaque commemorating the work of Sir Gilbert Barling, the first chairman of the Birmingham branch of the British Empire Cancer Campaign A second plaque, commemorating a gift of £30,000 from Alfred and Ruth Bullock towards the cost of the laboratories, was unveiled by Dr O Muhlbock of the Dutch Cancer Institute, Amsterdam

University of Durham

On July 4 and 5 the following degrees and diplomas were conferred

M D—G S Anderson, *Gordon Pringle, *G A Stirling
M B, B S—John Anderson, W V Anderson, Margaret S Atkins, Judith C H Bullen, Margaret S Burrill, Mary Bynon, *P M Calamel, I G Campbell, John Cape, Jean Carr, Ben-Zion Chalk, J R Cox, W G Donald, C M Dunn, L E Dunn, Elizabeth Elliott, M A Ferri, Gerald Gill, C P Gillie, H L Goldwater, Ronald Heslop, D H Irvine, Fiona M Lehmann, Margaret A Lewis, Thomas Lind, J B McCafferty, A J McComas, C H McCulloch, Alastair Malcolm, P F Moran, J M Morrison, H N Murray, Harald Natvig, Sarah H J Nelson, S A Oduntan, I, L T Oluwole, Alan Poweny, D G Proudler, D N Raine, Donald Rankin, M F Reece, Ernest Ross, Dorothy A Stevenson, J R C Stubbs, Margaret A Stubbs, Ernest Taylor, I H Taylor, Stanley Tetlow, Jean B Thompson, P R Uldall, Michael Ward, Joan M Whitmore, P G Wood, P H Yorke

* In absentia

D P H—Jean M Bainbridge, Florence Cadogan, Marion Harrison, T W L Knaggs, June K Lloyd, R T Pagan, Doris Story
D P M—Edmond Stanley Lower

University of Liverpool

Dr W E Kershaw has been appointed to the Walter Myers and Everett Dutton chair of parasitology and entomology, on the retirement of Prof R M Gordon

Dr Kershaw, who is 47 years of age, graduated M B from the University of Manchester in 1935, and four years later was awarded a junior research fellowship in tropical medicine with the Medical Research Council During the late war he served with the R N V R at sea and later as pathologist to the Royal Naval Auxiliary Hospital in Ceylon In 1946 he was appointed lecturer in medical parasitology in the Liverpool School of Tropical Medicine In 1949 he took the degree of M D with commendation He was awarded the Chalmers medal of the Royal Society of Tropical Medicine and Hygiene in 1955, and the following year graduated D SC Last year he was appointed Leverhulme senior lecturer in parasitology at the school He has made annual visits to the Cameroons and Nigeria for some years in connection with the helminthiasis research scheme of the Colonial Medical Research Council, and he represented the school at the World Health Organisation conference on onchocerciasis at Leopoldville in 1954

University of Glasgow

On June 18, the D P H was awarded to the following

R E Atkinson, D B Campbell W MacD Campbell, A J Childs, Margaret J Devine, D E Donald, Margaret E Forbes, G S Henderson, A S L Kennedy, J E Lunn, Marion T Lunn, Archibald McCutchion, Sheila Macintyre, J B Morris, W M Prentice, Frank Slane, A McI Tait

National University of Ireland

Dr D K O'Donovan has been appointed to a senior professorship of medicine and Mr Patrick Fitzgerald to a senior professorship of surgery at University College, Dublin

Royal College of Surgeons of England

At a meeting of the council held on July 10 Sir James Paterson Ross was re-elected president of the college Sir Archibald McIndoe was re-elected, and Mr A Dickson Wright was elected, vice-president Dr Warren H Cole, of Chicago, and Dr Charles W Mayo, of Minnesota, were admitted as honorary fellows Dr H J Windsor, of Brisbane, was admitted to the fellowship, as a member of 20 years' standing A diploma of fellowship was granted to R M Wagh

Dr Geoffrey Organe was coopted to the council as a representative of anæsthetics Dr Ivan Magill, Dr R J Minnitt, Dr E S Rowbotham, Sir Henry Souttar, and Dr R M Waters were elected honorary fellows in the Faculty of Anæsthetists

The following lecturers were elected for the coming year

Hunterian professors —W E Tucker, traumatic syndrome phases and stages, R A Mogg, congenital anomalies of the urinary tract, E M Nanson, tumours of the parotid gland, J B Curtis, subarachnoid hæmorrhage and intracranial aneurysms, C J Kaplan, conservative therapy in skeletal tuberculosis, P H Jones, lobectomy and bronchial anastomosis in the surgery of bronchial carcinoma, G J -Hadfield, hormone deprivation in breast cancer, A G Parks, microanatomy of the breast, T J S Patterson, congenital deformities of the hand, J W Dickson, pathological ossification in nervous disease, Cyril Harvard, non-malignant bile-duct obstruction, A J Davies, carcinoid tumours, G S M Botha, the closing mechanism between stomach and œsophagus and its importance in surgery of the gastroœsophageal junction, J S Calnan, surgical treatment of speech disorders

Arris and Gale lecturers —E R Smith, anatomy and physiology of the bile and pancreatic ducts, G L Bourne, anatomy, physiology, and pathology of the human amnion and chorionic membranes, K M Backhouse, the gubernaculum testis Hunteri, testicular descent, and maldescent

Erasmus Wilson demonstrators —Richard Goodbody, K M Laurence, L W Proger, R C B Pugh, H A Sissons, M A Skelton

Arnott demonstrators —Jessie Dobson, A A Barton, Alan Howe, R J Last, R M Livingston, Bertie Cohen

Buckston Browne dinner —At this dinner on July 9 the toast of The College was proposed by Mr Derek Walker-Smith, Minister of Health, who laid stress on the importance of a positive approach to the health and wellbeing of the nation and especially the industrial population, as a means of improving the general standard of life Sir James Paterson Ross, the president, emphasised in his reply that research has a direct application to the practice of medicine and the alleviation of disease, it is like a tree with many branches Sir Archibald McIndoe welcomed The Guests, among whom were many leaders of the medical and industrial worlds Responding, Sir Harry Jephcott spoke of the college's worldwide reputation and of its valuable contribution to public as well as medical work

Royal College of Physicians of Ireland

On July 4 the following were admitted to the licentiateship of the college

J A Aziz, G O Balogun G A Bharmal, N P Boyle, D C P Brown, J J V Caraher, F B A Coker, D P Connolly, Josephine P Cummins, D A F Doherty, J F Doyle, P A Egbe, M J Fennell, J G A Fitzgerald, Eithne M A Flood, Gabriel Blankson-Hemans, J T Hogan, Mary C Horgan, O G L Hunter, J H Jackson, A M Jeeva, Mary J Keating, Mary P R Kenny, N M N Lamki, Trevor Morgan, Jack Mullins, J F X McGlade, Ina L McGregor, Peter McLean, P R P Naidu, B R O B Nation, M J Noronha, Catherine O Connor, Eamon O Daly, C M Omarjee, R J Osborne, Mary Owens, Richard Quirke, S D Ram, D F Reynolds, Dolly T Salami, S K Suleman, Dzintars Svenne, J B Swan, W H Twedell, T R Vij, P B Vilain, F G Walls, L A G Wharton, L R L Whitelocke, T A Worth, Paul Zamick

Society of Medical Officers of Health

Scottish Branch —Dr I A G MacQueen has been elected president

Chartered Society of Physiotherapy

This society will hold its annual conference at Bristol from Sept 11 to 13 The society welcomes doctors to any of the lectures, and complimentary tickets may be had from the registration secretary, physiotherapy department, Bristol Royal Infirmary

Fellowships at the University of Rochester

Buswell fellowships are offered to medical graduates for research in any department of the school of medicine and dentistry Graduates of British medical schools are eligible.

Junior fellowships will be awarded to medical graduates who have completed at least one year of internship or equivalent training Research experience is not required but will be of advantage, since fellows are expected to spend about 90% of their time in research or in advanced study in preparation for research They provide a basic stipend of $4500 to $6000 a year and may be renewed with increments for a second or third year An additional $350 a year may be provided for each dependent

Senior fellowships will be awarded to medical graduates who have held a junior fellowship for two or three years or have had comparable experience in medical research and wish to continue in an academic career They will provide a basic stipend of $5500 to $8000 a year, with provision for annual increments and dependants

Applications will be received at any time, and forms may be had from Dr L E Young, University of Rochester Medical Center, 260, Crittenden Boulevard, Rochester 20, New York

College of General Practitioners

Public Welfare Foundation Prize Competition 1958 —The college will award six prizes of £40 in a competition open to senior students of all medical schools in the United Kingdom and Eire The closing date for entries is Aug 1, and application forms may be had from deans of medical schools or from the college, 41, Cadogan Gardens, London, S W 3

Postgraduate Medical School of London

A symposium, for consultant physicians, on rheumatic fever and rheumatic heart-disease will be held from Sept 22 to 25 at the school, Ducane Road, W 12, and at the Canadian Red Cross Memorial Hospital, Taplow, Bucks The fee for the course is £4 4*s* and applications should be made by Aug 14 to the dean of the school

International Congress of Leprology

This congress, which was to have been held in New Delhi, is now to meet in Tokyo on Nov 12 under the sponsorship of the Japanese Leprosy Foundation and the International Leprosy Association The secretary of the association (8, Portman Street, London, W 1) asks all who will be able to attend the congress in its new location to let him know at once

Rochampton Courses on Artificial Limbs

The next courses on artificial limbs and rehabilitation after amputation for orthopædic surgeons will be from Oct 13 to 17 inclusive, and the next for specialists in physical medicine on Oct 29 and 30 Those interested should apply to the Principal Medical Officer, Artificial Limbs and Appliances Centre, Roehampton House, London, S W 15

Diary of the Week

JULY 20 TO 26

Tuesday, 22nd

SOCIETY FOR THE STUDY OF ADDICTION
8 P M (11, Chandos Street, W 1) Mijnheer H J Krauweel (Amsterdam) Incidence and Treatment of Alcoholism in the Netherlands

Wednesday, 23rd

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
2 P M Dr Janet Niven Cytopathological Aspects of Latent Infection
INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, W C 1
5 P M Dr Willis J Potts (Chicago) *Congenital Atresia of the Œsophagus* (Alex Simpson Smith lecture)

Thursday, 24th

WEST LONDON HOSPITAL MEDICAL SCHOOL, Hammersmith, W 6
5 P M Mr Harold Burge Problems in Gastric Surgery (Alex Simpson Smith lecture)

Friday, 25th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
4 30 P M Dr Potts Respiratory Emergencies in the New Born (Moynihan lecture)
ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS, 58, Queen Anne Street W 1
5 P M Mr James Black (Johannesburg) *Reminiscences of Fifty Years' Medical Practice—Forty-Seven of Them in South Africa* (William Meredith Fletcher Shaw lecture)

The Lancet · Saturday 26 July 1958

CHILDREN IN HOSPITAL *

R S ILLINGWORTH
M D Leeds, F R C P , D P H , D C H
PROFESSOR OF CHILD HEALTH IN THE UNIVERSITY OF SHEFFIELD

SINCE Bakwin (1942) wrote on the loneliness of children nd Edelston (1943) on the results of separating them om their parents, much has been said about the psychogical effect of admitting them to hospital Among nportant papers are those of Powers (1948), Bowlby 1951), Jackson et al (1952), Prugh et al (1953), Capes 1955), Ylppo et al (1956), and Gofman et al (1957)

Exaggeration of Effects

On one hand, there is a tendency in some quarters to xaggerate the psychological trauma Prugh et al (1953), or instance, wrote that " most of the children showed daptive difficulties which persisted for weeks or months fter". I agree with Bowlby et al (1956) who, after a arefully controlled study of 60 children under 4 years of age spending a long period in a sanatorium, concluded that " Some of the workers who first drew attention to the dangers of maternal deprivation resulting from separation have tended on occasion to overstate their case In particular, statements implying that children who experience institutionalisation and similar forms of severe privation and deprivation in early life commonly develop psychopathic or affectionless characters are incorrect "

If this is true of long-continued institutional care, it is much more likely to be true of a short stay in hospital Exaggeration of the risk of harm can cause much unnecessary anxiety in parents and even delay necessary hospital treatment It can also lead other people to minimise this risk or even deny its existence

At the Children's Hospital, Sheffield, we follow up all children who have been discharged from the medical wards, in my experience it is exceptional for a child, on return home, to show behaviour problems which can be directly ascribed to his stay and experiences in hospital The only examples of severe persistent behaviour problems which I have been sure resulted from psychological trauma in hospital were in children who had been in long-stay orthopædic hospitals or infectious-diseases hospitals, in which no visiting was allowed

It is, of course, true that children cry in hospital Illingworth and Holt (1955) found that the majority of young children cry when their parents leave at the end of visiting-time, and that the majority show some emotional disturbance while in hospital, but that is quite different from suggesting that the experience of hospital commonly leads to behaviour problems which persist for weeks or months after discharge

Minimisation of Effects

On the other hand, some people tend to minimise the psychological trauma This tendency is seen especially among those who oppose daily visiting of children in hospital

Some time ago I set the following question in a pædiatric examination paper for nurses " Discuss the causes of crying in children in hospital " I was told that this was a most unfair question to set, because nurses had no experience of the problem, " for children do not cry in children's wards" I have heard it said that Robertson's film *A Two-year-old Goes to Hospital* gives an entirely untrue idea of what happens in a children's ward and is a gross exaggeration of the truth—a view with which I disagree

It would be indeed surprising if small children were not upset by admission to hospital They are particularly firmly attached to their parents in the first three or four years, and at no time do they feel the need of their parents' comforting love more than when they are feeling poorly It is unfortunate that it is just at this time that they are liable to be separated from their parents by admission to hospital Anyone, furthermore, is less adaptable when ill.

I imagine that every pædiatrician has seen behaviour problems which seemed to be directly ascribable to a period in hospital, and no-one could fail to observe the fretting and misery shown by some small children in hospital The problem of psychological trauma to children is real, and the fact that only a small minority show any ill effects after discharge must not lead us to minimise it Obviously we ought to do all we can to reduce such trauma, and to make the children's stay a happy one

Nature of Reactions

Short-stay Hospitals

At all ages, some children seem to be quite unaffected by admission to hospital they settle immediately and seem to be perfectly happy With young children, however, this is exceptional, the following reactions are commonly seen

(1) Persistent or frequent crying, and calling out for the mother Crying on departure of the parents after visiting-time

(2) Subdued and abnormally quiet behaviour in a child normally boisterous and happy

(3) Subdued and quiet behaviour until an attendant, doctor, or nurse approaches, when crying starts

(4) Subdued and quiet behaviour until the parents come, when crying starts

(5) Poor appetite, and in infants a failure to gain weight, despite absence of causal disease

(6) The development of enuresis or aggressiveness, mostly after a fairly prolonged stay

It is difficult to say with certainty what the child is thinking One feels that some small children are not altogether convinced that their stay in hospital is only temporary, and foolish statements to a child that he will " go home tomorrow ", when that is quite untrue, are bound to make him more and more sure that he is being left permanently in hospital I remember as a student being asked pitifully by a small boy " Doctor, when will it be tomorrow ? " He had been told repeatedly that he would go home tomorrow, but because of his illness (osteitis in pre-penicillin days) tomorrow was a very long time in coming

Long-stay Hospitals

The symptoms resulting from long separation from parents in the first three or four years have been adequately described by Bowlby (1951) and Robertson and Bowlby (1952) In an institution the predominant ones are quiet subdued behaviour and lack of spontaneous play and gaiety These children are " too good ".

I shall never forget a visit to a home for illegitimate children in a foreign city In a first-floor room were 20 or 30 children, aged 1 to 4 years, sitting on the floor like Madame Tussaud's figures they were quite still and were not laughing, crying, or talking There was no furniture in the room, apart from cots with solid wood sides which prevented the children in them from seeing out There were no toys On floor level there was an open french window, with nothing to prevent a child from falling out on to the concrete path below, but when a psychiatric friend of mine and I exclaimed about this, we were told that no child ever had fallen out We doubted whether one ever would the effects of emotional deprivation were so gross that the children did not move

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* A lecture given to the Central Council for Health Education, Jan 23, 1958

There have been several papers about behaviour problems in children on return home from hospital The symptoms include regression to infantile behaviour, such as enuresis and excessive clinging, fear reactions, including night terrors, and negativistic reactions and signs of insecurity, such as temper tantrums, speech disturbances, and destructiveness

The late psychological effects of a long stay in hospital have been amply discussed by Bowlby (1951)

Ætiology

A big difficulty in considering this subject is to know how much of the crying or abnormal behaviour observed should be ascribed to the hospital experience and how much to the parents

Parental factors which may lead to or aggravate psychological trauma in children are

(1) Any disturbance of the parent-child relationship before admission or after discharge from hospital There is no doubt that the better this relationship and the more secure the child, the less likely is he to be significantly disturbed by a spell in hospital Before ascribing his crying in hospital and other bad behaviour to the trauma of his hospital experience, one needs to know what the child is like at home, and how he behaves there

(2) Lack of preparation or inadequate preparation of a child for admission when he is old enough to understand

(3) *Unwise or excessive preparation* by the parents as a result of anxiety about the effects of admission, and transference of parental anxiety to the child

(4) Threats made by the parents that if the child does not do what he is told he will no longer be loved, will be changed for another child, will be taken to the doctor, or, worse still, taken to the hospital and left there

(5) Lack of daily visiting by the parents when visiting is allowed This will be referred to later

(6) Transference of parental anxiety to the child during a visit Unwise remarks and promises by the parents during visiting-time which cannot be kept—e g, concerning the day of returning home

(7) Parental attitudes on discharge of the child These include spoiling the child, with overindulgence and indiscipline, especially when he has recovered from a dangerous illness

Apart from this, it is very hard to decide whether behaviour problems are due to the hospital experience or not In the first place, all children have behaviour problems, and the fact that a problem develops after a spell in hospital does not prove that it is due to the stay in hospital Secondly, it is easy to ascribe bedwetting after discharge from hospital to psychological trauma, when in fact it is due to failure of the nurses to attend to the child's toilet needs In hospital it is easy to have wet nappies and sheets washed, and this, combined with a shortage of nurses, may lead to neglect of a child's toilet needs Thirdly, as Ylppo *et al* (1956) point out, parents who have been pleased with the recovery of a child in hospital are not so likely to blame the hospital for a child's bad behaviour as are parents who have been in some way dissatisfied, or have disliked a ward sister, or have had other complaints It is very difficult to arrive at the

Lastly, children may have been alarmed, before by foolish remarks by their school friends, who provided them with lurid and totally incorrect of operations

We may summarise the relevant factors thus

(1) The age of the child The younger he is the greate the risk of psychological trauma

(2) The length of his stay in hospital The shorter the st the less likely is he to suffer any lasting psychological harm

(3) The *parent-child relationship at home*

(4) The nature of the experiences in hospital

(5) The nature of the illness (The significance of this uncertain)

(6) The personality of the child This very important fac is apt to be forgotten It is easy to ascribe a child's undesir behaviour to mismanagement at home when in fact it is due due to inherited personality characteristics Whether h personality depends on hereditary or environmental facto it is almost bound to have a bearing on his response to h experiences in hospital

(7) The preparation of the child for hospital and the attitu of the parents on his discharge

Beneficial Effect of Admission to Hospital

Of the many papers on the effects of hospital children, hardly any mention the psychological advantage Yet there is no doubt that many children benefit fro their experiences They profit from the companionsh of others, from the making of new friends, from the wi guidance of doctors and nurses (especially if they ha some disturbance of behaviour before admission), an from the learning of independence Ylppo et al (195 carefully observed 50 children under the age of 7 wh were admitted for minor operations They found th adverse changes after discharge were exceptional, an that behaviour improved in many Some were mor "irritable" after discharge than they had been befor admission, but an equal number were less so Ylpp et al remark that "the favourable effect of the hospital isation in the social behaviour of many children deserve special attention"

Prevention of Psychological Trauma

AVOIDANCE OF UNNECESSARY ADMISSIONS

The more efficient an outpatient department the fewe children will be admitted to the wards from it Ther are few special investigations which cannot be done i the outpatient department, though some children ma have to be admitted simply because they live a long wa from the hospital In my experience it is only rarel necessary to admit a child "for observation" or "fo assessment"—e g, for behaviour problems, menta deficiency, and cerebral palsy

Children are still admitted to hospital, especially lon stay hospitals, because of primary tuberculosis This i occasionally necessary for social reasons, but there is n special treatment which is given in hospital for thes children which cannot be given at home

One feels that fewer children should be admitted t hospitals for infectious diseases Except when there ar difficult social circumstances, the great majority of case of uncomplicated measles and scarlet fever should b nursed at home If there are other children in the hous they will have been exposed to the infection before th infected child was sent to hospital, so isolation wi achieve little Furthermore, it is irrational to sen children with scarlet fever to an infectious-disease spital while other children with streptococcal tonsillitis e nursed perfectly well at home

More effective use of the public-health services, in- uding especially health visitors and home helps, can do uch to prevent unnecessary admission to hospital—at ormous saving of expenditure, apart from the advantage the child Immunisation against infectious diseases, ich as whooping-cough and poliomyelitis, can be xpected to do much to reduce hospital admission They ay also be reduced by home-care schemes, such as that stablished many years ago by the Leeds Public Dispensary nd Hospital, and the one developed later by St. Mary's Iospital, London

PREPARATION FOR ADMISSION

If a child is old enough to understand, he should be old a little of what he will see in hospital—about caps nd gowns, nurses and doctors, and so on He should be varned that he may be put into a cot, even though he has ong since graduated to a bed, for otherwise he may be adly offended It would often be of value to allow the hild to see the ward and meet the ward sister before his dmission Various hospitals have prepared pleasant ooklets which can be shown to the child, and some of hem are suitable for crayoning They include the Hospital of the South Bay, California, the Health Centre, Vancouver, the County Hospital, Lincoln, and the Whittington Hospital The Central Council for Health Education publishes a leaflet for the purpose There is good scope for more really pleasant booklets on the subject

Preparation of the child must not be prolonged or excessive, neither must it be neglected The difficulty is in striking the happy mean, and it is very much a matter of opinion In general, I feel, two or three days' preparation should be adequate Too long or excessive conversation about the hospital is apt to cause anxiety in the child It is quite wrong to go into *details* of operations, such as tonsillectomy, which are quite beyond the child's comprehension and can only lead to unpleasant fantasies and fears in an imaginative child The emphasis should be on the pleasant side of hospital life rather than the unpleasant experiences which the child may face

In some research projects (e g, Albany) a social worker has visited the home on several occasions to prepare the child This would hardly be practicable in ordinary hospital practice

A leaflet for the parents can be of some value It should describe visiting-times, the purposes of the visit, the importance of not making promises (about the child's return home) which will not be fulfilled, the provision of suitable toys, and the sending of letters by parents and friends

ADMISSION PROCEDURE

It should never be necessary to drag a screaming child away from his mother in the casualty or outpatient department The mother should go up to the ward with her child and see him into bed, if possible staying a short time with him until he has had a chance to see his new surroundings Ideally a child who is well enough should be admitted not to the ward but to the ward playroom The traditional bath on admission can sometimes be avoided The child should take with him his favourite teddy, bit of rag, or toy The immediate [illegible] his clothes may cause anxiety

THE TYPE OF HOSPITAL

Whenever possible, a child should be admitted to a children's hospital rather than to a general hospital This is obviously impossible if the town is not large enough to justify a separate children's hospital The advantages of a children's hospital compared with a children's ward in a general hospital are numerous there are fewer changes of nurses, the nurses are trained in children's work, including the psychological aspects of children's nursing, there will probably be better toys and play equipment, occupational therapists and members of all the ancillary services, such as physiotherapy and speech therapy, are more accustomed to work with children, and the laboratories are likely to use micromethods instead of those requiring more venepunctures

For these and many other reasons there is everything to be said for a separate children's hospital—preferably very near an adult hospital, so that there is constant contact between the two hospitals I agree entirely with the report of the Royal College of Physicians (1957) which said "There is no doubt that special children's hospitals offer the best service for children, because the staff, at all levels, and in all departments, is attuned to the special needs of the sick child"

Except where it is really necessary, children should not be admitted to infectious-diseases hospitals Each [illegible] hospital and each children's hospital should have its own isolation unit, where cases of infectious disease [illegible] and where children requiring specialised [illegible] those with gastroenteritis) can be treated [illegible] with experience of these problems The [illegible] Physicians report stated that "in every [illegible] isolation accommodation is essential, [illegible] developed a block should be included [illegible] We all know, furthermore, that a [illegible] children admitted to infectious [illegible] suffering from infectious disease [illegible] understand why so many cases [illegible] meningitis are sent to them.

Children should certainly [illegible] wards This is particularly [illegible] Physicians report. [illegible] things which they should [illegible] logical trauma, the [illegible] adult patients and [illegible] have an adequate [illegible] tional therapy and [illegible] a children's [illegible] other children

If there [illegible] should be a [illegible] is no [illegible] is [illegible] of [illegible]

In general, children should not be admitted to single cubicles, except where there is a special reason for it—e g, infectious disease—and even then there may be several children with the same infection who can be together in a small ward Cubicles are desirable for babies but undesirable for older children unless the circumstances are exceptional Children are far happier in a ward with other children than in a room of their own in a private block or in a nursing-home (On seeing a depressed-looking boy in a single room in a private block, a consultant remarked to his resident "Poor little rich boy,") The aim of cubicles is the prevention of cross-infection We all know how regrettably they fail to achieve this Apart from this, one has to balance the risk of cross-infection against the psychological trauma of solitary confinement If a cubicle has to be used, the glass should reach down to the child's eye level, so that he can see others from where he lies in bed

If a child has to be admitted to a hospital a second time, he should be admitted to the same hospital and to the same ward as before A combined medical and surgical ward helps to make this possible It helps the child, because he knows the sister in charge

Transfers of children to other hospitals for specialised treatment are difficult to avoid but should be kept to a *minimum The difficulty lies in the expense of providing* specialised equipment in more than one hospital in a group In a city, however, much can be done by concentrating children in one children's hospital, rather than in several scattered units none of which are large enough to justify the provision of equipment and personnel for the various subspecialties

Each children's unit should have accommodation for mothers, as advocated by the late Sir James Spence, so that a mother can be admitted with her child if she is particularly disturbed about being separated from him, or if he is likely to find the separation difficult, or if a child who has been admitted is not settling down satisfactorily This arrangement presents great psychological advantages to mother and child The mother nurses her own child under supervision and is helped by the confidence so acquired The arrangement is especially useful in the care of difficult feeding problems, in which a mother has lost confidence in her ability to feed her baby

When I told a mother that I wanted to admit her 3-year-old child, she said that she would give anything and do anything, such as scrubbing the ward floor, to be allowed to come in with her child I told her that she could have a room with her child without having to scrub the floor, but that she would help to nurse the girl Her gratitude was immense

Unfortunately, because of domestic difficulties, relatively few mothers can come into hospital with their child Moreover, when pressing them to come, one must remember the possible psychological trauma and jealousy in the children left behind, and balance it against the psychological trauma in the sick child if the mother does not come in with him Those left behind must not be forgotten

If a mother cannot stay the night, she can often come in for the whole day to look after and be with her child The provision of home helps should make this more easy

DAILY VISITING

All children's units should allow daily visiting There are still hospitals, particularly long-stay ones, which oppose it, mostly on the grounds that separation from the parents does no harm, and that children settle down better if not visited Their attitude arises largely failure to understand the psychological reactions children I have seen severe psychological problem lasting for years in children who have been in such long-stay hospital where visiting was not allowed each case the children, who were inpatients at the age 3 to 4, bore considerable *resentment against their parent* reminding them for several years that they "deserted" them when they were ill I heard of a 4-year-old chil who was an inpatient for ten *months in an infectiou* diseases hospital without being allowed to see his parent By the time he did see them he must have complete forgotten them

Some infectious-diseases hospitals have rigid rule about visiting Parents may be allowed to look at a chil through a glass partition This must be very tantalisin for a small child, who cannot understand why the parent do not enter the room I can see no reason why parent should not be allowed into the room of a child wit measles, and the same applies to most of the othe common infectious diseases

The arguments usually raised against daily visiting an the risk of cross-infection, the difficulty of one child no having a visitor when others do, and the idea that th child is upset by visits and is better without them A *for the first, several studies have shown that daily visitin* does not increase cross-infection The difficulty of one child not having a visitor when others do is a real one and difficult to answer, *but I do not agree* with the ide that there should be equal misery for all Tactfu handling by the nurses, with the traditional kindness o other visitors who see a child looking lonely, will hel such children As for the third objection, it is true tha most young children cry when their parents depart, bu this lasts only a short time, and it is far better tha children should be disturbed for a few minutes on th departure of their parents, with the certain knowledge (which they very soon acquire, even when very young that the parents will come every day, than that they should become more and more convinced that they have been deserted, or are being punished

In leaflets or booklets given to them by the hospital, parents may be told so much about the importance of daily visiting that they feel guilty when they cannot visit every day *In a previous paper* (Illingworth and Hol 1955) we pointed out that visits are often costly and take much time, and this must apply more in long-stay hospitals Parents can be helped to pay their fares by the almoner's department, but there is the real problem of the children at home Home helps, supplied by the health authority, may be part of the solution Once more one has to strike a balance between the psychological trauma and jealousy in the normal siblings at home and the needs of the sick child in hospital

The visits should preferably be in the evening, nea the child's bedtime, and should not be too short, but there should be considerable latitude for the sake of those *whose* work or domestic situation makes this difficult

For children spending a very long time in hospital occasional weekends at home are of considerable value

HOSPITAL DESIGN

We have much to learn from other countries—in particular, I would say, from Finland—about the design of children's hospitals The provision of a veranda for each bed, as at The Hospital for Sick Children, Great

Ormond Street, London, is desirable Ideally, each ward would have a playroom, or a combined eating-room and playroom It is necessary to give thought to making the outpatient, casualty, and X-ray departments attractive and colourful The latter department may be frightening for a child something can be done by pictures and toys to make it more attractive Large waiting-halls should be a thing of the past A small attractively equipped and decorated waiting-room in between each two consulting-rooms is much better Pleasant canteen facilities should be provided When parents who have attended a morning outpatient clinic with a child are asked to stay for another clinic in the afternoon, meals should be provided

INSTRUCTION OF NURSES AND STUDENTS

On the psychological aspects of child care nurses should get instruction from the pædiatrician and not from a sister-tutor who is divorced from practical ward work They should learn about the psychological development and management of normal children and the psychological needs of the sick child

Nurses should be told about their role as temporary mother-substitutes and be encouraged to pick children up, instead of turning a deaf ear to their crying They must be told that the small child who stands at the end of his bed with his nappie half-down his legs and with a running nose, screaming all day long, is not a naughty spoilt child but a normal one, and that the quiet subdued 2-year-old who lies in bed all day without a murmur is not being "good" (when he is normally a boisterous, noisy, happy child) but is showing an abnormal and undesirable reaction as a result of emotional deprivation They must be told to avoid such errors as forcing food, taking the temperature by the rectal route, giving an enema before an operation, making a fuss about an "accident", or giving children unsuitable clothes, such as a girl's nightie for a 10-year-old boy, or a pyjama jacket without pyjama trousers They must be told about the importance of attending to children's toilet needs (just as one would at home), of keeping them occupied, of arranging them in suitable age-groups (particularly the older children), and of seeing that when they have to be readmitted they come back to the same ward as before They must be told about the importance of never lying to a child (especially in saying that a painful procedure, such as an injection, will not hurt), and of telling him what is going to happen—not long before, but just before it is done In fact, nurses have to be instructed in all the points mentioned in this paper

KEEPING CHILDREN OCCUPIED

Nurses should be instructed in the selection of toys and books for different age-groups At the Children's Hospital, Sheffield, they all receive a lecture and practical demonstration on the subject They should be told about the importance of seeing that the children have plenty to do They should be brought to realise that a well-managed children's ward should be thoroughly untidy

I have been impressed in travels abroad by the lack of provision of toys for children in hospitals In this country the provision of toys for the younger children is apt to receive insufficient attention

Every children's ward has its 240-piece jigsaws and books about naughty girls at school who turned out well, but one rarely sees wards equipped with 10-piece or 20-piece jigsaws, with dolly-dressing equipment, or with books suitable for the child aged 5 to 6 who has lately learnt to read. Furthermore, a nurse who has been properly instructed should be able to advise parents about toys and books suitable for children Parents are apt to bring mechanised toys, often quite expensive, which are of little value to a child, because they give no scope to his imagination I have dealt with the question of toys for different age-groups elsewhere (Illingworth 1957)

It would be a good thing to have one person, perhaps someone in the department of occupational therapy, who would go round every ward every day with a trolley-load of toys She would take responsibility for them and try to reduce the prevalent high loss-rate Another, perhaps a nursery-school teacher, might be responsible for the children's books, advising on their purchase and taking them round to the wards Voluntary workers could well take up this pleasant occupation

For children who are sufficiently well, out-of-doors equipment—e.g, sandpit, climbing-frame, and wheeled vehicles—could be provided A roof garden might be used for the purpose

A department of occupational therapy, in which nurses receive instruction as part of their training, is an essential part of a children's hospital The occupational therapist must avoid the temptation of concentrating on the older children, who are better able to look after themselves than are the younger ones The occupational therapist should be on call for any newly admitted child or any child who is unhappy New admissions should be seen by the occupational therapist as soon as possible after coming to the ward—not next day

Teachers are now provided by the education authority in most children's units in this country These teachers greatly help children in hospital by keeping them occupied and preventing psychological trauma as a result of backwardness on return to school They teach short-stay children as well as long-stay ones

I feel that a doctor should be responsible for supervising the arrangements and the supply of suitable and adequate toys for the children The matter is of considerable psychological importance, and, if he does not take an interest in the matter, it may well be that no one else does

A television set in each ward is appreciated

PROVISION OF SUITABLE FOOD

A resident doctor should be expected to keep an eye on the food supplied to children Imagination is required to make food attractive in appearance and palatable for children Too often the child is expected to enjoy a nondescript mush, or a daily diet of minced meat and mashed potatoes, followed by milk pudding Among other items a liberal supply of fresh fruit and ice-cream is likely to be welcomed, and chips are usually popular

UNPLEASANT PROCEDURES

By a little thought much can be done to minimise unpleasant procedures For instance, when one is about to give an injection or to take blood for a laboratory investigation, the preparations for the prick should be concealed from the child One sees a child wincing at the sight of the needle and syringe being made ready By judiciously standing with one's back to the child and between the child and the syringe, he can be prevented from seeing the preparations Much can be done by getting the equipment ready in another room before approaching him

There is a tendency to carry out many investigations one after the other, all requiring pricks, instead of doing a batch at one time from one specimen A little forethought will prevent such a succession of investigations and avoid those which will throw no light on the problem

In the same way a succession of anæsthetics can often be avoided Venepunctures for laboratory investigations may be done when the child is under an anæsthetic for another purpose

The era of painful daily dressings has now largely gone, and wounds are given a chance to heal without being damaged by daily interference Few unpleasant experiences in hospital can have caused so much psychological trauma as they did There is still room for thought, however, about the avoidance of such painful procedures, or about the use of a tranquillising drug when a painful procedure is necessary in an anxious child

Now that depot penicillins and more satisfactory oral preparations are available, repeated injections of aqueous penicillin should be a thing of the past, except in certain rare special circumstances The increasing use of micromethods is reducing the number of venepunctures in children's hospitals, but some hospitals have a long way to go in their use

The use of premedication before anæsthesia is a matter for further investigation

There are advantages and disadvantages which cannot be discussed here There is much truth in the comment by Jackson et al (1952) that "our experience has shown that the child best able to meet the hospital-anæsthesia-surgery situation is the child who is able to trust the physician and nurses to treat him fairly", and "the child who is anxious and suspicious is the child who will cry and resist the most" Nevertheless, one has to try to reduce psychological trauma in children who are insecure as a result of unsatisfactory home relationships or who are of a nervous type, and for them premedication may be advisable It may help to allow a child to take his favourite toy to the anæsthetic room There is a great need for careful experiments of the "blind" variety to determine the best method of preparing children for anæsthesia

Trauma from mechanical procedures can be reduced by the appointment of doctors for resident appointments who have had previous appointments in adult wards

SIGHTS AND SOUNDS

Children in a ward should not be allowed to see another child suffering, to see death, to see unpleasant procedures being applied to another child, or to see a child bringing up blood after a tonsil operation The proper use of a treatment room, and the use of a cubicle for a dangerously ill child, will prevent much of this

Great care should be taken to avoid talking in front of children about their ailments It is very easy to err in this direction during a ward round It is a mistake to think that the use of long words provides safety in this direction Children hear and misinterpret what they hear I saw a boy who had been seriously disturbed because he had been told (in an adult ward) that the patient in the next bed to his was not going to get better An inexperienced nurse could easily say this without thought

One must remember the foolish conversation in a ward between one child and another Hence all the children should be prevented from seeing and hearing things which they should not hear, because otherwise details of unpleasant happenings or sayings will soon be embroidered and exaggerated, and so lead to anxiety

CONFINEMENT TO BED

It is difficult to determine why children are kept in bed so long in many illnesses The most likely explanation in many cases lies in the fact that no-one has thought of getting them up The number of medical conditions demanding strict confinement to bed is very small indeed

A high proportion of children in the medical wards have been admitted because of respiratory infections There is no justification for keeping them in bed after their temperature has become normal or nearly so Gibson (1956) conducted an interesting study of the effect of rest in bed on children with these infections at home Those who were up and about their room, in spite of slight pyrexia, fared quite as well as those who stayed in bed A child who is feeling poorly because of an infection wants to be in bed and should stay there, whereas a child who is anxious to get up should usually be allowed to do so A child is far happier if allowed to sit in a chair near a fire, playing games with other children, and having his meals out of bed, than if he is confined to bed all day In any case an active child who is feeling well is likely to exert himself much less if allowed to sit at a table in the ward than if he is restlessly jumping about in the bed Children, like adults, much prefer to go to a lavatory than to be compelled to use a bedpan, and few medical conditions necessitate the deprivation of the right to go to the lavatory The children's doctor should pay special attention to the question of stay in bed

ROLE OF THE FAMILY DOCTOR

In many practices family doctors visit their patients in hospital Children who know the doctor are helped in this way The doctor, furthermore, helps the parents by reporting progress and confirming what they have been told themselves

THE ROLE OF THE PADRE

The hospital padre can help to reduce psychological trauma in children by talking to them and by holding ward services There should be contact between the padre and the parents of the children

EARLY DISCHARGE

With care and thought the duration of stay in hospital can be greatly reduced below its present figures, particularly if proper use is made of the public-health services, including the health visitor and the district nurse In my opinion a constant conscious effort should be made to reduce hospital stay At the Children's Hospital, Sheffield, when a child is admitted for operation on an inguinal hernia, he is admitted in the morning, operated on in the afternoon, and discharged home next day

The problem of carriers of pathogenic intestinal organisms, such as those of Sonne dysentery and the salmonella group, should be considered by the public-health authorities The problem involves the long stay in hospital of otherwise perfectly well children

DISCUSSION WITH THE PARENTS ON DISCHARGE OF THE CHILD

All parents should be seen by the doctor during the child's stay in hospital and on his discharge Not only must they be told about his illness but also they need to be advised about possible difficulties in behaviour They must be warned not to spoil him because he has recovered from an illness, he must be treated as a normal child and subjected to the same discipline as anyone else Anxiety must not be shown if he wets his bed They must be told that, if any regression symptoms or symptoms of insecurity appear—clinging, temper tantrums, fears or sleep disturbances—they should be tackled by treating the basic cause, the feeling of insecurity Every effort should be made to give the child a feeling of importance and of being wanted and loved, reprimands being absolutely avoided if possible

The doctor should always make sure that the parents have had a full opportunity to ask any questions they wish

AVOIDANCE OF PARENTAL TRAUMA

This indirectly benefits the child The role of accommodation for the mother in a room with her child, arrangements for the mother to stay during the day, and of daily visiting have already been mentioned The admission procedure is also important the avoidance of trauma to child and mother by separating a crying child from his mother in the outpatient department has been emphasised

Mothers should not be expected to witness unpleasant procedures I heard of a mother being asked to hold her child down while painful daily dressings were made It is doubtful whether a mother should see her child coming out of an anæsthetic, particularly after tonsillectomy, though it has psychological advantages to the child

Good liaison between parents, nurses, and doctors achieves a great deal in the reduction of trauma Parents should always feel that they can obtain all the information they want, and that they know what is being done and going to be done Above all things, nurses and students must be taught never to tell a mother that she is being "fussy" or "overanxious" A good mother *is* anxious about her child

REFERENCES

Bakwin, H (1942) *Amer J Dis Child* 63, 30
Bowlby, J (1951) Maternal Care and Mental Health Geneva
— Ainsworth, M, Boston, M, Rosenbluth, D (1956) *Brit J med Psychol* 29, 211
Capes, M (1955) *Bull Wld Hlth Org* 12, 427
Edelston, H (1943) *Genet Psychol Monogr* 28, 1
Gibson, J P (1956) *J Pediat* 49, 256
Gofman H, Buckman, W, Schade, G H (1957) *Amer J Dis Child* 93, 157, 629
Illingworth R. S (1957) The Normal Child London
— Holt, K S (1955) *Lancet*, ii 1257
Jackson, K, Winkley, R., Faust, O A, Cermak, E G (1952) *J Amer med Ass* 149, 1536
Powers G F (1948) *Amer J Dis Child* 76, 365
Prugh D G Staub, E M, Sands H H, Kirschbaum, R. M, Lenihan, E A (1953) *Amer J Orthopsychiat* 23 70
Robertson, J, Bowlby, B (1952) *Courr Centre Enfance*, 3, 131
Royal College of Physicians (1957) Report on the Care of Children in Hospital see *Lancet* (1957) i, 926
Ylppö, A., Hallman, N, Landtman, B, Pupari, R. (1956) *Ann Pædiat fenn* 2, suppl 8, p 3

GOITRE AND ARTERIOSCLEROSIS

Unto Uotila
M D
PROFESSOR OF FORENSIC MEDICINE

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Our interest in the ætiology and pathogenesis of arteriosclerosis and atherosclerosis was aroused by our observation at forensic necropsies that persons who had died from coronary sclerosis often had a goitre We have had the principal organs weighed over a period of several years and have been able to demonstrate that goitre is in fact significantly commoner in people who have died of coronary sclerosis than in those who have died from other causes

Much has been published on the connection between the thyroid gland (especially in hypothyroidism) and experimental atherosclerosis (Andrews 1953, Katz and Stamler 1953) It shows that in hypothyroidism there is not only hypercholesterolæmia but also a tendency to arteriosclerosis, and that thyroid hormone can decrease both exogenic alimentary cholesterolæmia and atherosclerosis There is also some clinical and postmortem evidence of a tendency to atherosclerosis in *myxœdema* (Fishberg 1924, Rosenthal 1934, Bruger and Rosenkrantz 1942, Means 1948, Kountz 1950), though some workers, such as Andrews (1953), have thought this inconclusive

The relationship of goitre and coronary sclerosis has been discussed in listing the indications for goitre resection in the presence of coronary-artery disease But we have found no reference in the literature to the possible ætiological relationship of the two conditions

TABLE I—WEIGHT OF ORGANS

—	Coronary-sclerosis group	Controls	P
Height (cm)			
Males	168·0±0 49	169 6±0 48	>0 1
Females	156 2±0 96	158 5±0 71	0 05<P<0 1
Body-weight (kg)			
Males	68 8±0 93	65 6±0 81	0 02
Females	64 2±1 97	63·4±2 02	>0 6
Pituitary gland (g)			
Males	0 45	0 44	
Females	0 53	0 54	
Thyroid gland (g)			
Males	50 3±2 1	37 8±1 3	0 001
Females	46 6±3 5	35 0±2 7	0·01
Adrenal glands (g)			
Males	11 45±0 20	12 0 ±0 26	0 05<P<0 1
Females	10 05±0 42	10 57±0 39	>0 2
Gonads (g)			
Males	34	35	
Females	5 13	5 98	
Pancreas (g)			
Males	92	89	
Females	72	71	
Heart (g)			
Males	435± 6 6	395± 5 8	0·001
Females	421±11 4	360±10 8	0 001
Brain (g)			
Males	1503± 8 7	1455± 9 1	0 001
Females	1286±13 7	1286±13 5	>0 5
Liver (g)			
Males	1831±22 8	1685±25 0	0 001
Females	1724±52 6	1508±43 6	0·01
Spleen (g)			
Males	140 3±3 9	136 0±8 7	>0·4
Females	139 4±7 8	120 9±7 9	>0 4
Kidney (right) (g)			
Males	161 6±2 19	150 1±2 26	0 001
Females	128 1±2 69	112 7±3 39	0 01
Prostate (g)	21	26	

Material and Methods

250 deaths from coronary sclerosis and its consequences were selected from the material of the Institute of Forensic Medicine at Helsinki, 200 of them in men and 50 in women In another 200 men and 50 women selected as controls the causes of death were either natural or violent —the only principle observed in the selection being to obtain a case as free as possible from coronary sclerosis This involved the examination of thousands of cases Each age-group of 5–10 years included equal numbers of coronary-sclerosis deaths and controls

In each case all the principal organs were weighed after careful preparation A thyroid gland weighing more than 40 g was regarded as a goitre because this seems to be the natural limit in Finland where goitre is of medium endemicity (Wahlberg 1938, Uotila 1942)

Results

The height of the patients in the coronary-sclerosis group did not differ statistically from that of the controls, but on the average they were somewhat shorter (table I) The coronary-sclerosis males tended to be heavier than their controls, but no significant difference was found in body-weight in the women The weight of the men with coronary sclerosis and goitre, however, was significantly heavier than the men with coronary sclerosis but no goitre (P=0 002)

TABLE II—FREQUENCIES OF SOME CHANGES

—	Coronary-sclerosis group (%)	Controls (%)	P	
Goitre (thyroid more than 40 g)				
Males	58	28	0 0005	0 0005
Females	50	22	0 0005	
Sclerosis of aorta				
Males	84	45	0 001	0 001
Females	98	60	0 001	
Cerebral sclerosis				
Males	34	22	0 025	0 025
Females	70	48	>0 1	
Nephrosclerosis				
Males	9	4	0 025	0 005
Females	32	12	0 025	
Cholecystopathy				
Males	7	4	>0 5	0 4
Females	26	20	>0 4	

The weights of the pituitary gland, the adrenal glands, the gonads, the pancreas, and the spleen of the coronary-sclerosis group did not differ significantly from those of the controls (table I) The thyroid gland, on the other hand, weighed more in the coronary-sclerosis group The incidence of goitre (i e , thyroid gland weighing more than 40 g) was 58% for coronary-sclerosis males against 28% for male controls, and 50% for coronary-sclerosis females against 22% for female controls The difference was statistically very highly significant (table II)

As the coronary-sclerosis group and the controls were matched for age, there was no difference in their average ages The average age both of the coronary-sclerosis males with goitre and of the coronary-sclerosis males without goitre was 55 The χ^2 test of the cumulative percentage age-distribution showed a difference for the men in the over-65 group (P=0 02) In the women, the average age of the goitrous coronary-sclerosis case was 65 and of the non-goitrous coronary-sclerosis case 68, the difference of age-distribution in the χ^2 test being statistically significant (P=0 001)

That the heart weighed more in the coronary-sclerosis group than in the controls was to be expected, but it is significant that it weighed more in the goitrous coronary-sclerosis cases than in the non-goitrous (P=0 002)

The liver and the kidneys of the coronary-sclerosis group were heavier than those of the controls, but there was no correlation between their weight and the presence or absence of goitre Finally, mention must be made of the higher incidence of general arteriosclerosis in the coronary-sclerosis group compared with the controls (table II)

Discussion

It is easy to understand that coronary sclerotics are somewhat shorter and heavier than other people, because most patients with coronary sclerosis belong to Kretschmer's pyknic type The fact that coronary sclerotics with goitre weigh more than those without goitre suggests that the thyroid gland may be responsible The finding that in coronary sclerotics the heart is bigger in those with goitre than in those without goitre points in the same direction If the thyroid is involved in the ætiology of coronary sclerosis, is this through toxicity of the thyroid secretion or hypofunction of the gland, or some factor not yet known ?

The heavier liver and kidneys of coronary sclerotics are usually explained by stasis due to heart-failure, but this explanation seems somewhat lame when one finds no corresponding increase in the weight of the pancreas and the spleen

As coronary sclerosis and arteriosclerosis are largely concomitant, it is justifiable to identify them to some extent

We considered the possibility that the high incidence of an abnormally large thyroid gland (i e , goitre) could result from stasis, but we concluded that this is extremely unlikely, since the weight and incidence figures of goitre and coronary sclerosis bear too significant an interrelationship The age-distribution of goitrous and of non-goitrous cases of coronary sclerosis supports this conclusion A more specific relationship is also indicated by the influence of goitre on the weights of the body and of the heart in cases of coronary sclerosis Finally, our view is supported by the fact that the iodine content of food is smaller (Vilkki 1956, Roine et al 1958) but coronary sclerosis more common (Keys et al 1958) in eastern Finland, where endemic goitre is more prevalent (Wahlberg 1938) than in western Finland

The close association between goitre and arterio-sclerosis suggests a causal relationship It might be thought that coronary sclerosis, through the stress it originates, causes involution of the thyroid gland and produces colloid goitre (Selye 1950, Isotalo), but this explanation seems rather far-fetched, especially in the light of the facts about goitre in Finland which we have just mentioned

The association between coronary sclerosis and goitre can, we think, be explained differently The Finnish *endemic goitre is hypoepithelial—i e , in 60%* of cases its *content of epithelium is less than 25%, owing to abundant* colloid and fibrosis (Saarenmaa 1956) Furthermore, it is usually nodular In the Joensuu district in eastern Finland the level of protein-bound iodine in the serum was 2–3 μg per 100 ml in 6 1% of those with goitre and 2–4 μg in 21 3% (Jussila) The corresponding figures for Helsinki are 5 3 and 18 1% respectively (Lamberg et al 1956) Also in view of the fact that goitre (i e , thyroid gland weighing more than 40 g) occurs in 45% of all the necropsy material of the Institute of Forensic Medicine, *Helsinki, it is probable that endemic goitre in Finland has some hypothyroid features*

In hypothyroidism an excessive amount of thyrotrophic *hormone is secreted In addition* to its stimulating effect *on the thyroid gland, thyrotrophin affects* connective tissue directly by increasing its mucopolysaccharide content (Asboe-Hansen and Iversen 1951) It also prevents the maturation of granulation tissue whereas growth hormone promotes it (Saikku 1956) We think it likely that the acknowledged tendency of hypothyroid patients to arteriosclerosis is attributable not only to raised serum-cholesterol level but also to the overproduction of thyrotrophin

It is generally believed that endemic goitre is caused by hypertrophy and involution, this means, at some stage or other, overproduction of thyrotrophin According to Lamberg et al *persons with goitre in the* Aaland Islands have a greater amount of pretibial acid mucopolysaccharides than do healthy persons, and this might be attributable to overproduction of thyrotrophin

Summary

Postmortem findings in *250 persons who died* of coronary sclerosis are *compared with the findings* in 250 persons *who died from other* causes

Goitre was commoner, and the average weight of the thyroid was higher, in those with coronary sclerosis *Among the coronary-sclerosis* cases, those with goitre had a tendency to lower average age at death and a higher average heart-weight

Comparison of body-build showed that the 250 persons with coronary sclerosis were slightly shorter and heavier than the controls Among those with coronary sclerosis those with goitre were heavier than those without goitre These findings are correlated with observations made in Finland on the nature and distribution of endemic goitre, the iodine content of the food, and the distribution of coronary sclerosis

It is concluded that goitre and arteriosclerosis may have a pathogenetic relationship, possibly through hypothyroidism and the overproduction of thyroid-stimulating hormone by the pituitary gland

This work was aided by an institutional grant from the Damon Runyon Memorial Fund for Cancer Research, New York (DRG 290 A/T), from the Sigrid Juselius Foundation, Helsinki, and from the Natural Science Research Council, Helsinki, to the Institute of Forensic Medicine, University of Helsinki

REFERENCES

Andrews, E C (1953) *Circulation*, 7, 437
Asboe-Hansen, G , Iversen, K. (1951) *Acta endocr , Copenhagen*, 8, 90
Bruger, M , Rosenkrantz, J A (1942) *J clin Endocrin.* 2, 176
Fishberg, A M (1924) *J Amer med Ass* 82, 463
Isotalo, A In preparation
Jussila, R In preparation
Katz, L. N , Stamler, J (1953) Experimental Atherosclerosis Springfield, Ill
Keys, A , Karvonen, M J , Fidanza, F (1958) *Lancet*, ii, 175
Kountz, W B (1950) *Arch Path* 50, 573
Lamberg, B A., Wahlberg, P , Forsius, P I (1956) *Acta med scand* 154, 201
— — Wegelius, O , Hellstrom, G In preparation
Means, J H (1948) The Thyroid and Its Diseases Philadelphia
Roine, P , Pekkarinen, M , Karvonen, M J , Kihlberg J (1958) *Lancet*, ii, 173
Rosenthal, S R. (1934) *Arch Path* 18, 827
Saarenmaa, E (1956) *Acta chir scand* suppl 207
Saikku, L A (1956) *Ann Med exp Fenn* 34, suppl 10
Selye, H (1950) The Physiology and Pathology of Exposure to Stress Montreal
Uotila, U (1942) *Arb path Inst Univ Helsingf* 10, 391
Vilkki, P (1956) *Ann Acad Sci fenn* ser A, no 71
Wahlberg, J (1938) *Acta med scand* suppl 94

DIET AND CARDIOVASCULAR DISEASE IN FINLAND

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In the epidemiology of cardiovascular disease Finland is of special interest (Keys et al 1958) because the mortality of men from coronary disease is higher there than in any other European country, and mortality and disability statistics suggest that cardiovascular disease is more prevalent in the eastern than in the western part of Finland Keys et al (1958) have also shown that serum-cholesterol levels in Finland are unusually high, particularly in the eastern part Since there is much evidence that diet plays a part in the ætiology of coronary disease, it is important to get reliable information about the diets in these areas and, in particular, to know if dietary differences can be related to different incidences of coronary disease Dietary surveys were therefore made in selected areas of West and East Finland in connection with the medical studies of Keys et al (1958)

TABLE I—ANALYSIS OF FAMILIES INCLUDED IN FINNISH DIETARY SURVEY

—	1956		1957	
	East	West	East	West
Number of families	42	42	20	20
Mean number of persons in each family	4 3	4 4	3 9	4 1
Mean age of adult men (yr)	40 4	39 7	45 3	38 9
Mean age of adult women (yr)	41 0	38 8	43 0	40 8
Mean age of those younger than 20 (yr)	8 1	8 0	9 7	8 1

The greater part of the dietary survey was made in June, 1956, but to get some idea of the seasonal variations half the families were studied again in January, 1957 Forty-two families from the West and the East, mainly of farmers of fair financial standing, were included in the study Almost all the men in the families did heavy physical work (grades 3 and 4) The number of people in the families was 358 (0 7–0 8% of the population of the communities)

TABLE II—SERUM-CHOLESTEROL LEVELS (MEAN ± STANDARD ERROR) OF MEN IN DIETARY SURVEY COMPARED WITH THOSE IN ENTIRE MATERIAL (KEYS ET AL 1958)
(All samples were taken in September, 1957)

Group	Age (yr)			
	20–29	30–39	40–49	50–59
East				
Men in dietary survey	226±23 9 *(4)*	252±16 7 *(12)*	247±16 3 *(13)*	250±21 2 *(11)*
Men in work grades 3 and 4	215±6·9 *(40)*	263±8 0 *(57)*	251±5 9 *(57)*	252±7 6 *(31)*
West				
Men in dietary survey	220±24 3 *(4)*	222±11 2 *(17)*	248±14 8 *(13)*	279±19 3 *(7)*
Men in work grades 3 and 4	204±7 1 *(50)*	223±5 2 *(52)*	239±7 4 *(48)*	248±7 5 *(39)*

Numerals in parentheses denote number of persons

The groups of families in each area were matched as closely as possible A comparison of the groups is presented in table I

An attempt was also made to select the families in the dietary survey to represent the same populations as in the serum-cholesterol study (Keys et al 1958) The extent to which this was achieved may be judged with the aid of the serum-cholesterol levels, a comparison of the men in the dietary survey with those in the larger group is

TABLE III—AMOUNTS OF MAJOR FOODSTUFFS CONSUMED IN WEST AND EAST FINLAND
(g per caput per diem)

Foodstuff	Summer 1956		Winter 1957	
	West	East	West	East
Bread				
Soft	199	267	204	269
Dry	41	26	29	23
Flour	55	47	51	56
Potatoes	224	175	224	220
Other vegetables	43	13	83	28
Fruits and berries	41	28	71	45
Margarine	10	6	13	7
Vegetable oil	0	0 2	0	0 4
Sugar	66	57	52	65
Milk				
Whole	612	670	562	677
Skimmed	144	274	90	138
Butter	37	49	31	45
Cheese	14	12	20	3
Meat				
Beef	14	11	21	19
Pork	14	11	22	25
Other	5	8	6	29
Sausage	30	21	30	13
Fish	25	50	13	20
Eggs	23	10	21	4

TABLE IV—AMOUNTS OF PROTEINS, FATS, CARBOHYDRATES, AND CALORIES IN DIETS OF WEST AND EAST FINLAND
(Per caput per diem)

—	Summer 1956			Winter 1957		
	West	East	P	West	East	P
Proteins (g)	78 6	86 9	0 05	79 1	82 9	>0 25
Fats (g)	99 3	102 7	>0 25	98 9	105 0	>0 25
Carbohydrates (g)	357	348	>0 25	346	376	>0 25
Total energy (kcal)	2598	2636	>0 25	2549	2732	0 25
Energy from proteins (%)	12 1	13 2		12 4	12 1	
Energy from fats (%)	34 4	35 0		34 9	34 6	
Energy from carbohydrates (%)	53 5	51 8		52 7	53 3	

presented in table II, which shows that the serum-cholesterol levels of the men in the dietary survey do not differ significantly from those of the men in the larger groups

The distribution of food items within each family was not studied The men's share of the food consumed was naturally more than the average for each member of the family, and there may have been some selection of food items within each family Nevertheless the qualitative character of the diet of a family probably is a satisfactory indicator of the diet of the men

The food consumption was determined by weighing—i e, special investigators weighed during seven days all the items used in the preparation of foods, during meals, and between meals, as well as refuse and table waste

TABLE V—LIPIDS IN DIETS OF WEST AND EAST FINLAND
(Per caput per diem)

—	Summer 1956			Winter 1957		
	West	East	P	West	East	P
Animal fats (g)	83 3	91 2	0 1	81 5	90 5	0 25
Vegetable fats (g)	16 0	11 5	0 001	17 4	14 5	0 25
Fatty acids (g)						
Saturated	53 0	56 5	0 25	52 3	56 5	>0 25
Mono-enes	33 6	33 9	>0 25	33 7	35 5	>0 25
Linoleic	6 7	6 3	0 25	6 8	6 8	
Other poly-enes	1 2	0 9	>0 25	1 3	1 2	>0 25
Cholesterol (mg)	402	375	>0 25	383	363	>0 25

Accurate information about the foods actually consumed was thus obtained

The figures of food consumption, which give an idea of the Finnish dietary in general, are shown in table III A comparison of the figures for the West and those for the East shows, among other things, a higher consumption of bread, milk, butter, and fish in the East, and of vegetables, margarine, and eggs in the West

The calorie values of the diets, as well as the amounts of protein, fat, carbohydrate, calcium, iron, vitamin A, aneurine, riboflavine, nicotinamide, and ascorbic acid, were calculated according to Finnish food consumption tables (Turpeinen and Roine 1952) For iodine recent analytical values of foodstuffs in West and East Finland were available (Vilkki 1956) In the calculation of fatty acids of butter fat Finnish values of Peltola (1944) were used Fatty-acid figures for most typical margarines used in the country were obtained from analyses kindly mad by the Research Division of the Miami Valley laboratorie of the Procter and Gamble Company in U S A Othe nutrients were calculated according to estimates fixe after an extensive survey of the literature

Table IV shows that the amounts of proteins are usuall large, and there seems to be a significant differenc between West and East in the summer survey Th energy values are in all cases very much alike A high percentage of energy, about 35%, is derived from fats,

TABLE VI—AMOUNTS OF SOME AMINOACIDS, VITAMINS, AND MINERALS IN DIETS OF WEST AND EAST FINLAND
(Per caput per diem)

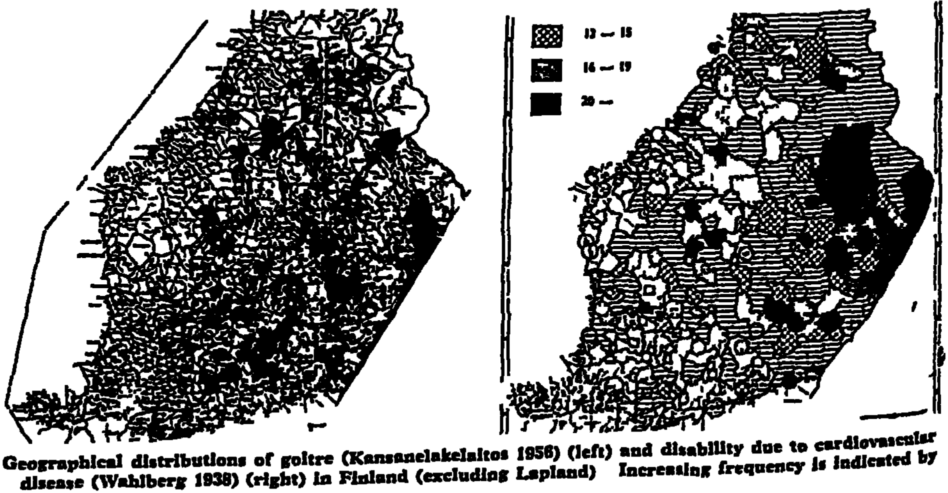
—	Summer 1956			Winter 1957		
	West	East	P	West	East	P
Cystine (g)	0 84	0 88	>0 25	0 83	0 88	>0·25
Methionine (g)	*1 66*	*1 71*	*>0 25*	*1 69*	*1 69*	
Vitamin A (I U)	2840	2780	>0 25	3270	2820	0·1
Vitamin E (mg)	9 90	9 21	0 1	11 10	9 73	0·05
Thiamine (mg)	*1 51*	*1 53*	*>0 25*	*1 57*	*1 69*	>0·25
Riboflavine (mg)	2 33	2 74	0 01	2 26	2 48	0·25
Nicotinamide (mg)	12 1	11 5	>0 25	12 8	13 6	>0 25
Pyridoxine (mg)	2 89	3 08	0 25	2 79	3 04	>0 25
Pantothenic acid (mg)	6·41	6 50	>0 25	6 28	6 45	>0 25
Choline (mg)	695	645	0 1	734	668	*0 25*
Ascorbic acid (mg)	56	46	0 002	68	*54*	*0 05*
Calcium (mg)	*1199*	*1406*	*0 01*	*1204*	*1219*	*>0 25*
Iron (mg)	11 7	11 9	>0 25	12 4	12 5	>0 25
Iodine (µg)	71	55	0 001	62	51	0 02

but there are practically no differences between West and East in this respect and no seasonal differences either

Table V shows that more vegetable fats were consumed in the West than in the East, in summer the difference was highly significant Because the vegetable fat is mainly margarine, this difference has, however, very little effect on the fatty-acid values Saturated acids were consumed somewhat more in the East and linoleic acid and other poly-enes in the West, but differences are not significant A noteworthy fact is the large intake of saturated acids compared with the small intake of poly-enes, in the West this ratio is 6 6, in the East 7 5 The " cholesterogenic" formula (Keys et al 1957)

$$x = 2 \times g \text{ saturated fatty acids} - g \text{ poly-enes},$$

gives x=105 8 (1956) and 105 0 (1957) for the East, and x=98 1 (1956) and 96 5 (1957) for the West



Geographical distributions of goitre (Kansanelakelaitos 1956) (left) and disability due to cardiovascular disease (Wahlberg 1938) (right) in Finland (excluding Lapland) Increasing frequency is indicated by darker shade

Hence the dietary fat may be expected to raise the serum-cholesterol level higher in the East than in the West, which is in agreement with the actual observations (Keys et al 1958)

Figures for some aminoacids, vitamins, and minerals are given in table VI, which shows that there are no significant differences between West and East in the intakes of cystine and methionine or of most of the vitamins and minerals Ascorbic acid, however, was obtained in significantly greater amounts in the West—and vitamin E, at least in winter, too Riboflavine and calcium, on the other hand, were obtained in summer in greater amounts in the East

The iodine content of the diets deserves special attention All the iodine intakes are low, and there is a highly significant difference between West and East—findings which agree well with those of Virtanen and Virtanen (1940) and Vilkki (1956) Endemic goitre is common in Finland, particularly in the East At least a part of this goitre is of hypothyroid type (Uotila et al 1958) Since hypothyroidism raises the serum-cholesterol level, the low iodine content of the diet may contribute to the high serum-cholesterol values in Finland in general and in East Finland in particular The geographical distributions of goitre and of disability due to cardiovascular disease (see figure) show in Finland a striking parallelism The necropsy findings of Uotila et al (1958) also support the hypothesis that lack of iodine and resulting goitre are involved in atherogenesis in Finland

Summary

To find out if the higher incidence of cardiovascular disease in East compared with West Finland is due to dietary differences, dietary surveys were made in two selected areas of the country The food consumption during seven days of eighty-four families in summer and forty families in winter was determined by accurate weighing, and the daily calories and nutrient intakes per caput per diem were calculated

The average amount of fat consumed each day was 98 9 g–105 0 g per caput, being very similar in West and East and in summer and winter The mean percentage of energy derived from fats was within the limits of 34 4% and 35 0% The intake of saturated fatty acids was a little larger in the East, and that of linoleic acid and other poly-enes in the West, but these differences were not statistically significant In both cases the intake of saturated acids compared with that of poly-enes was rather large The ratio of saturated acids to poly-enes was higher in the East than in the West

Considerable differences were found in the amounts of iodine, ascorbic acid, and vitamin E, the intakes of which were significantly larger in the West The low iodine content of the diet, causing hypothyroidism and thus a rise in the serum-cholesterol level, might be partly responsible for the high serum-cholesterol levels and coronary mortality in Finland in general and in East Finland in particular

REFERENCES

Kansaneläkelaitos (1956) Kertomus Kansaneläkelaitoksen XVIII Toimintavuodelta. Helsinki.
Keys, A., Anderson J T Grande F (1957) *Lancet*, ii, 959
— Karvonen M. J., Fidanza, F (1958) *ibid.* July 26, p 175
Peltola E. (1944) Helsinki thesis
Turpeinen O., Roine P (1952) Ruoka-ainetaulukko Helsinki
Uotila U, Raekallio, J Ehrnrooth W (1958) *Lancet*, July 26, p 171.
Vilkki P (1956) Helsinki thesis
Virtanen A I Virtanen, E (1940) *Acta med scand* 105 268
Wahlberg, J (1938) *ibid.* suppl. 94

SERUM-CHOLESTEROL STUDIES IN FINLAND *

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MORTALITY ascribed to cardiovascular, particularly to coronary, disease is higher in Finland than in other European countries (Kannisto 1951, World Health Organisation 1953) A very high incidence of coronary disease is shown by hospital admissions in Finland (Keys 1957) Arteriosclerotic heart-disease appears to be particularly common in East Finland, regional differences within Finland are indicated both by mortality-rates (Kannisto 1947) and by the statistics of the Finnish National Pension System on disability (Kansaneläkelaitos 1956) Fig 1 illustrates geographical differences within Finland in mortality ascribed to cardiovascular disease among men aged 30–59 Table I shows the morbidity-rates

The data on Finland, in which the population is predominantly engaged in agriculture and lumbering, are surprising in view of the widespread belief that coronary disease is relatively uncommon in physically active rural populations In Finland coronary disease is common among farmers and woodcutters Preliminary surveys in East Finland recently disclosed that myocardial infarction accounts for about 10% or more of male patients in the medical departments of hospitals caring for the rural population This finding and the morbidity-rates in table I stimulated a closer examination of the situation in rural East and West Finland with attention to the diet and the serum-cholesterol levels

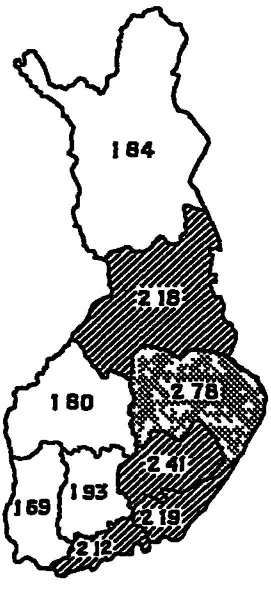

Fig 1—Mortality ascribed to arteriosclerotic heart-disease (International List, Sixth Revision, nos. 420–422) in Finland (V Kannisto, unpublished)

Investigation

In the autumn of 1956 a field study was made in West Finland and in Karelia, the areas where the records show the greatest differences in the incidence of coronary disease In addition, in Helsinki, the fire brigade and a group of "directors" (business and professional men)

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* This study was supported by grants from the Science Board of the State of Finland, from the Sigrid Jusélius Stiftelse, from the Finnish Heart Association, from the National Dairy Council (Chicago), from the Winton Companies Fund (Minneapolis), and from the American Heart Association.

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TABLE I—FINNISH PENSION SYSTEM 1955 MORBIDITY-RATES OF MALES, PER 1000 INSURED, ON ACCOUNT OF CORONARY DISEASE, HYPERTENSION, AND OTHER HEART-DISEASES (KANSANELÄKELAITOS 1956)

District	Coronary	Hypertension	Other heart-disease
Helsinki	1 88	0 79	1 58
Kuopio	4 63	1 90	4 46
Turku	1 60	0 68	1 59

The populations considered here relate to Kuopio (East), Turku (West), and Helsinki Pension System Districts

were studied Altogether 976 clinically healthy men were examined, 869 being aged 20–59

In the rural areas names were drawn from a list of men of the desired ages in or accessible to the various preselected communities where local headquarters could be established Substantially all the men who were requested to appear for examination did so The Helsinki groups were less representative of that area The fire brigade was a preselected group, but self-selection within the brigade was not involved in the examinations The "directors" responded to invitation, few so invited refused, but bias from self-selection is not excluded from this group

Dietary surveys, which are separately reported, were made in both rural areas in June, 1956, and January, 1957 (Roine et al 1958) The serum-cholesterol levels of the adult members (about 160) of the households involved were measured then in addition to the main survey, reported here, in the autumn of 1957 The Helsinki studies were made in October and November, 1957

The programme included medical history, physical examination, anthropometric measurement, a 12-lead electrocardiogram, serum-cholesterol estimation, and a questionnaire about smoking The blood-serum was analysed for total cholesterol and for cholesterol in the α and β lipoprotein fractions separated by paper electro-phoresis (Anderson and Keys 1956) In a large number of samples the cholesterol was estimated both locally in the fresh material and in duplicates, air-dried on filterpaper, and flown to Minneapolis to assure full comparability with cholesterol values from other populations studied at, or similarly controlled by, the Laboratory of Physiological Hygiene

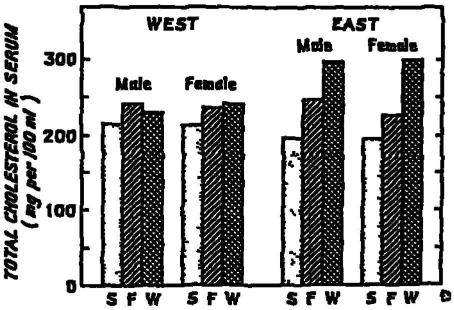

Fig 2—Seasonal variation in mean level of total cholesterol in serum of men and women in West and East Finland S, June, 1956; F, September, 1956, W, January, 1957

Results

Fig 2 shows the mean levels of total cholesterol in the serum of the persons of either sex in the dietary survey In the West the level rose significantly from June to September, but in the East this seasonal trend was larger and continued until January, when the average was about 100 mg per 100 ml higher than in June Accordingly, in comparing serum-cholesterol levels of populations, seasonal variations should be considered, at least in regions such as East Finland, where seasonal differences in climate and mode of life are extreme

The numbers of persons of given age, sex, and occupation are too small in the dietary survey to permit detailed analysis Table II summarises the serum-cholesterol levels of the 869 men studied in the autumn The rural men are classified according to level of occupational physical activity Grades 1 and 2 include sedentary and light work (clerks, teachers, car drivers, &c), and grades 3 and 4 cover hard to very hard physical work (farmers, blacksmiths, loggers, &c) On this scale the "directors" would be classed as grade 1 and the firemen as grade 2 or possibly between grades 2 and 3

The most obvious trend of the serum-cholesterol levels is that with age, the values for men in the twenties in all groups being lower than at older ages, the highest averages being in the forties in three groups, in the fifties in two groups, and in the thirties in the more active men in East Finland For the combined groups the mean serum cholesterol levels for successive decades of age are 212, 247, 257, and 258 mg per 100 ml This age trend is similar to that found elsewhere in populations characterised by relatively high serum-cholesterol levels (Keys et al 1950, Keys 1956)

TABLE II—MEAN TOTAL CHOLESTEROL (MG PER 100 ML) IN SERUM OF CLINICALLY HEALTHY MEN IN FINLAND CLASSIFIED BY DECADES OF AGE

Region and work grade	Age-group (yr)			
	20–29	30–39	40–49	50–59
East, grades 1 and 2	226±9 1 (28)	276±11 8 (24)	286±11 1 (24)	258±14 1 (14)
„ „ 3 and 4	215±6 9 (40)	263±8 0 (57)	251±5 9 (57)	252±7 6 (31)
West, grades 1 and 2	199±10 6 (17)	212±12 8 (15)	260±15 9 (11)	241±15 5 (7)
„ „ 3 and 4	204±7 1 (50)	223±5 2 (52)	239±7 4 (48)	248±7 5 (39)
Helsinki "directors"	222±26 8 (6)	246±6 9 (42)	267±10 5 (31)	250±15 7 (8)
Helsinki firemen	212±4 4 (63)	250±5 4 (86)	260±4 8 (92)	285±7 4 (27)

Numerals in parentheses denote number of men in group

Important regional differences were found At all ages and work grades the averages were higher for East (Karelia) than for West Finland, and these differences were particularly notable at ages over 30

These regional differences might be due to heredity or to environmental factors An attempt was made to elucidate the relative influence of these two factors by grouping the Helsinki subjects according to place of birth, firemen and "directors" being pooled because there is no statistical difference between them Three groups were made (1) those born in Helsinki and the surrounding county (Uusimaa), (2) those born in the four counties with the lowest mortality from cardiovascular disease among men aged 30–59 (fig 1), and (3) those born in the remaining counties or in the area ceded to the U S S R in 1940 and 1944—i e, Karelia

The mean serum-cholesterol levels of these groups are shown in table III No significant differences were found

TABLE III—MEAN TOTAL CHOLESTEROL (MG PER 100 ML) IN SERUM OF MEN IN HELSINKI CLASSIFIED BY AGE AND BY COUNTY OF BIRTH

County of birth	Age-group (yr)			
	20–29	30–39	40–49	50 59
Helsinki and other Uusimaa	209±6 3 (36)	253±6 8 (61)	260±6 5 (53)	268±12 8 (15)
Turku and Pori, Vaasa, Lappi, Häme	214±6 8 (14)	242±9 5 (24)	258±9 8 (32)	273±3 5 (8)
Kuopio, Mikkeli, Kymi Oulu, ceded area	213±9 0 (15)	248±8 5 (40)	272±7 8 (40)	268±19 1 (11)

Numerals in parentheses denote number of men in group

TABLE IV—MEAN TOTAL CHOLESTEROL (MG. PER 100 ML.) IN SERUM OF 786 FIREMEN IN DIFFERENT CITIES

City	Age-group (yr.)			
	20–29	30–39	40–49	50–59
Helsinki	212±4·4 (63)	250±5·4 (85)	260±4·8 (92)	255±7·4 (27)
Malmö	189±5·7 (34)	210±5·7 (47)	237±7·0 (38)	236±6·0 (31)
Naples	132±4·3 (33)	156±3·3 (41)	168±4·1 (71)	
Minneapolis	219±8·7 (18)	231±4·9 (74)	250±4·0 (103)	258±8·5 (28)

Numerals in parentheses denote number of men in group.

Thus it appears that the mean cholesterol differences between the population groups in East and West Finland are primarily determined by the mode of life and or other environmental factors. There are climatic differences between East and West Finland, but these are not great, both parts are subarctic with long cold winters and short cool summers.

The mean serum-cholesterol level appears to be somewhat related to the habitual level of physical activity among men aged 40–49. At older and at younger ages there were no statistically significant differences between activity groups, in the East the men in the less active occupations tended to have higher serum-cholesterol levels, while the reverse was true in the West, and neither of these trends is significant.

More detailed analysis will be made later as regards possible interrelations of serum-cholesterol levels with blood-pressure, relative obesity, body build, and electrocardiograms. The smoking history of the men is being analysed with the help of Dr. Esko Orma and Dr. Josef Brozek. So far it appears that, in all the groups, smokers tend to have higher serum-cholesterol levels than do non-smokers, but this relationship is not enough to explain the differences between the regions. The men in West Finland smoked less than those in the other groups.

TABLE V—MEAN LEVELS OF CHOLESTEROL (MG. PER 100 ML.) IN α-LIPOPROTEIN FRACTION OF SERUM IN MEN FOR WHOM TOTAL CHOLESTEROL AVERAGES ARE GIVEN IN TABLE II

Region and work grade	Age-group (yr.)			
	20–29	30–39	40–49	50–59
East, grades 1 and 2	41·8	46·3	46·0	45·7
,, 3 and 4	44·0	45·4	46·3	51·6
Helsinki directors	44·7	45·2	46·3	42·0
Helsinki firemen	46·2	45·3	45·9	46·8
West, grades 1 and 2	41·6	44·6	37·4	45·7
,, ,, 3 and 4	44·2	42·1	43·3	45·0

Other differences also were observed. The men in Helsinki tended to be tallest, those in East Finland shortest, and those in the West intermediate. Obesity was more common in the Helsinki groups than in the rural groups. Systolic blood-pressure tended to be highest in East Finland, lowest in Helsinki, and intermediate in West Finland.

Discussion

It is interesting to compare these findings in Finland with comparable studies in other populations. The averages at given ages are generally higher than in other populations studied by the same methods (Keys et al. 1957). Table IV compares men in the same occupation, full-time members of the city fire brigades in Helsinki, Malmö (Sweden), Naples (Italy), and Minneapolis (U.S.A.). Except at ages 20–29, where there is no significant difference between Helsinki and Minneapolis firemen, the Helsinki firemen have much higher serum-cholesterol levels than do the firemen in the other cities.

Similar differences between men of these populations appear when comparisons are made in other occupational categories (Keys et al. 1957). In general it seems that men in the populations studied in Finland have, on the average, higher total serum-cholesterol levels than do men studied elsewhere to date.

The differences in level of total cholesterol in the serum in the Finnish groups are due to cholesterol in the β-lipoprotein fraction separated by paper electrophoresis. Table v shows that the cholesterol level in the α-lipoprotein is substantially the same in all the groups, there are no statistically significant differences between any of the averages in table v.

The values for α-lipoprotein cholesterol in table v are comparable to those we have obtained in many other populations of men with both low and high serum-cholesterol levels and in dietary experiments in which the total serum-cholesterol level changed in response to alterations in the diet (Anderson et al. 1957, Keys et al. 1957). In clinically healthy men, at least, the levels of α-lipoprotein cholesterol show remarkably little variation, the mean values of groups and the means for many measurements on the same person seldom being outside the range of about 37–47 mg. per 100 ml. measured by our method.

TABLE VI—MEAN LEVELS OF α AND TOTAL CHOLESTEROL IN SERUM OF FARMERS' WIVES IN EAST AND WEST FINLAND

Group	α-cholesterol	Total cholesterol
20 East Finland women	56·2±3·5 (45·8)	237·7±12·2 (257)
28 West Finland women	56·7±1·6 (42·7)	227·0±7·5 (231)

Numerals in parentheses denote means for male farmers of same age in same area.

Women, however, usually have higher levels of α-lipoprotein cholesterol, though the level of total cholesterol in the serum tends to be similar to that for men of the same age in the same population. Data from East and West Finland (table VI) illustrate this point. Some farmers' wives accompanied their husbands and asked to be examined also. This was permitted for reasons of local public relations, and the serum-cholesterol levels of 48 women, aged 30–49, are summarised in table VI. The average levels of α-cholesterol in the serum in both East and West Finland are higher, and those of total cholesterol and, especially, β-lipoprotein cholesterol tend to be lower in women than in their husbands. The mean levels of β-cholesterol in the serum of men are 29·7 and 18·0 mg. per 100 ml. higher than in the women in East and West Finland respectively.

Summary

Statistics indicate unusually high mortality-rates and morbidity-rates in Finland as a whole, and in East Finland in particular, ascribed to coronary disease.

Total cholesterol and that in the α and β lipoprotein fractions were measured in 869 clinically healthy men aged 20–59 in the city of Helsinki and in two rural regions of Finland.

The total cholesterol levels tended to be higher than those observed in populations elsewhere, and this excess was accounted for by β-lipoprotein cholesterol.

Farmers' wives resembled the men in the rural areas as regards total chloesterol but had higher levels of α-lipoprotein cholesterol

In the age range 40–49 the men in occupations demanding heavy physical work had lower cholesterol levels than had the men in lighter work, but at other ages the cholesterol level appeared to be unrelated to habitual physical activity

Smokers tended to have higher cholesterol levels and lower blood-pressures than had non-smokers

At all ages and activity levels the men in East Finland tended to have higher levels of total cholesterol in their serum than had the men in West Finland, and this difference was entirely accounted for by β-lipoprotein cholesterol However, when the men in Helsinki were classified according to region of birth, there were no significant differences, suggesting that the regional differences are not due to hereditary influences

REFERENCES

Anderson, J T, Keys, A (1956) *Clin Chem* 2, 145
— — Grande, F (1957) *J Nutr* 62, 421
Kannisto, V (1947) The Causes of Death as Demographic Factors in Finland Helsinki
— (1951) *Duodecim Helsinki*, 67, 1108
Kansaneläkelaitos (1956) Kertomus Kansaneläkelaitoksen XVIII Toimintavuodelta Helsinki
Keys, A (1956) World Trends in Cardiology (edited by A Keys and P D White), vol I, p 134 New York
— (1957) *J Amer med Ass* 164, 1912
— Anderson, J T, Grande, F (1957) *Lancet*, ii, 959
— Mickelsen, O, Miller, E V O, Hayes, E R, Todd, R L (1950) *J clin Invest* 29, 1347
Roine, P, Pekkarinen, M, Karvonen, M J, Kihlberg, J (1958) *Lancet*, ii, 173
World Health Organisation (1953) Annual Epidemiological and Vital Statistics 1950 Geneva

ACUTE PEPTIC ULCERATION IN EMPHYSEMA

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Teare (1957) and Latts et al (1956) found a higher prevalence of peptic ulcer in necropsies of emphysema patients than might be expected in the general population In Teare's cases, which were all coroner's necropsies, the ratio of observed to expected ulcers or scars was 51/35 5 In the cases of Latts et al the prevalence of ulcer was 27%, which is at least three or four times the expected figure In contrast to Teare's cases many of these patients died from emphysema, and it can be assumed that many of them had been severely anoxic with right-sided heart-failure Fulton (1953) found peptic ulceration at necropsy in 9 out of 50 cases of cor pulmonale, but neither Bockus (1944) nor White (1951) observed an increased prevalence of ulcer in heart-failure, though mucosal venous engorgement was common

Referring to the work of Latts et al *The Lancet* (1956) commented that it would perhaps be wise to await confirmation of the possible connection between peptic ulceration and hypertrophic pulmonary emphysema before speculating on the cause The present study, based on necropsy material at the City General Hospital, Sheffield, was designed to elicit further information concerning this relationship

TABLE I—PREVALENCE OF PEPTIC ULCER IN CONGESTIVE HEART FAILURE 88 CONSECUTIVE NECROPSIES

—	Cor pulmonale			Other cases of heart failure		
	Males	Females	Both sexes	Males	Females	Both sexes
No examined	19	5	24	33	31	64
Peptic ulcer	7	3	10	2	1	3

Prevalence of Peptic Ulceration in Heart-failure

Between March 17, 1952, and March 16, 1953, 88 patients with heart-failure were examined post mortem All had had congestive heart-failure and had been thoroughly investigated in life, especially with regard to the incidence of cor pulmonale (Flint 1954)

The high prevalence of active peptic ulceration discovered at necropsy in cases of cor pulmonale (10 out of 24), in all of which there had been anoxic heart-failure due to emphysema, contrasted with a prevalence of 3 in 64 other cases of heart-failure (table I) In the cases of cor pulmonale, the ulcers were acute and usually multiple in 5 (all duodenal), chronic in 3, and combined in 2 In the other forms of heart-failure, chronic ulceration was observed in 3 cases, acute ulceration was not seen

None of the 7 patients with acute ulceration had complained of pain, but 4 died after a massive hæmorrhage Only 2 had received an oral antibiotic

Prevalence of Acute Peptic Ulceration in Emphysema

The above figures suggested that further information might be gained from a postmortem study of acute peptic ulceration Arrangements were therefore made for a special scrutiny to exclude such a condition at all postmortem examinations on patients over the age of 16 for a period of twenty-four months—April 1, 1954, to March 31, 1956 At the end of this period the postmortem reports were reviewed and the original clinical notes studied in every case of acute ulcer, of chronic lung disease, and of heart-failure Of 87 cases of diffuse emphysema acute peptic ulceration was found in 18 (21%), and of the remaining 1037 cases without emphysema in 17 (1 6%) (table II) The prevalence was a little higher in patients with cor pulmonale, all of whom had exhibited congestive heart-failure in life (column 1), than in the emphysema patients without heart-failure (column 2), but many of the latter had been anoxic The ulceration was usually situated in the pyloric region of the stomach and multiple

In the emphysema group evidence of bleeding was found in 8 cases at necropsy and in 3 others in life In 1 patient the ulcer had perforated 4 patients had collapsed from unsuspected hæmorrhage None of the 18

TABLE II—PREVALENCE OF ACUTE PEPTIC ULCERATION IN 1124 CONSECUTIVE NECROPSIES

—	Emphysema cases					Remaining cases		
	With heart-failure (cor pulmonale)		Without heart-failure		Both groups			
	M	F	M	F	Both sexes	M	F	Both sexes
Acute ulceration with hæmorrhage	5	1	1	1	8	2	5	7
Acute ulceration with perforation	1	0	0	0	1	1	0	1
Acute ulceration alone	4	2	2	1	9	3	6	9
Total	10	3	3	2	18*	6	11	17
No of cases examined	39	14	25	9	87	666	371	1037

* Site of ulceration in 18 emphysema cases duodenal 3 (single, 1, multiple 2), gastric 15 (single, 3, multiple, 12)

patients complained of ulcer dyspepsia, and an ulcer was suspected clinically in only 1 case

It can be assumed from a study of the clinical notes that all the patients with cor pulmonale had had profound hypoxia, hypercapnia, and acidosis, and most of them received treatment for a respiratory infection A tetracycline drug or chloramphenicol had been given orally to 9 of the 18 patients in whom acute ulceration was proved at necropsy, and to 27 of the 69 patients without ulceration It is therefore unlikely that the lesion had been caused by the irritant effect of the antibiotic on the gastric mucosa

Of 17 cases of acute ulcer not associated with emphysema, 5 were admitted to hospital because of bleeding In the remaining 12 cases, the following lesions were detected cerebral thrombosis (3), uræmia (2), mitral stenosis with heart-failure (3), lobar pneumonia (3), and hepatic cirrhosis (1)

An active chronic gastric or duodenal ulcer was found in 5 of the 87 emphysema patients

Discussion

In the first series here described, gastric and duodenal ulceration was detected at necropsy more frequently in patients who had died from cor pulmonale than in those who had died from other forms of heart-failure In the second series acute ulceration was found to be 13 times more frequent in cases of emphysema than in all the remaining cases submitted to necropsy

Most patients with emphysema had been severely anoxic—apparently because of respiratory infection Possible factors in the development of ulceration in cases of emphysema are (1) acute respiratory infection, (2) chronic respiratory infection, (3) drug toxicity, (4) derangement of the gaseous equilibrium of the blood, (5) a combination of these factors, (6) congestive heart-failure in combination with one or more of these factors, but not by itself, (7) the strain, mental and physical, of a long illness, (8) tobacco, dietary, and nutritional factors

An answer to this problem of ætiology has not been gained from the present survey In a controlled clinical investigation Allibone and Flint (1958) found that the prevalence of chronic bronchitis and of acute respiratory infection in patients admitted to hospital with acute perforation or hæmorrhage was similar to that for a control group of surgical emergencies, but only 2 patients had anoxic heart-failure Thus, the high incidence of peptic ulceration in emphysema is apparently restricted to fatal or severe cases The possible irritant effect of oral antibiotics can be discounted The factor common to all fatal cases of emphysema is the derangement of blood gases Browne and Vineberg (1932) showed that this could influence gastric secretion in animals, but knowledge of the influence of hypoxia and hypercapnia on human gastric secretion is lacking It is theoretically possible that this gaseous disturbance could either stimulate the secretion of gastric juice or impair the secretion of gastric mucus Experimental work in this field might yield useful information about the ætiology of peptic ulcer

Summary

88 patients with congestive heart-failure were examined post mortem Of 24 cases of cor pulmonale due to anoxic emphysema, 10 had peptic ulceration (7 acute), of 64 cases of heart-failure due to other causes, 3 had peptic ulceration (none acute)

In a second planned series of consecutive necropsies, which included all examinations in patients over 16 during a period of two years, there were 87 cases of severe emphysema (which in most cases was complicated by severe anoxia or pulmonary heart-failure) Acute ulceration was found in 18 (21%), against a prevalence of 17 (1 6%) in 1037 cases without emphysema

There appears to be a definite association between acute peptic ulceration and severe emphysema This may possibly be due to derangement of blood gases

We wish to thank our medical and surgical colleagues at the City General Hospital, Sheffield, for allowing us to peruse the case-notes of patients admitted under their care.

REFERENCES

Allibone A, Flint, F J (1958) *Lancet*, July 26 p 179
Bockus, H L (1944) Gastro-Enterology p 502 Philadelphia
Browne, J S L, Vineberg, A M (1932) *J Physiol* 75, 345
Flint, F J (1954) *Lancet*, ii, 51
Fulton, R M (1953) *Quart J Med* 22, 43
Lancet (1956) ii 240
Latts, E M, Cummins, J F, Zieve L (1956) *Arch intern Med* 97, 576
Teare, D cited by Avery Jones, F (1957) *Brit med J* i, 719
White, P D (1951) Heart Disease, p 620 New York

BRONCHITIS, ASPIRIN, SMOKING, AND OTHER FACTORS IN THE ÆTIOLOGY OF PEPTIC ULCER

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Flint and Warrack (1958) report the prevalence of acute peptic ulcer in over 1000 consecutive hospital necropsies For cases of generalised emphysema the figure was 21%, compared with 1 6% for the remaining cases without emphysema In a separate series of 88 consecutive necropsies in cases of congestive cardiac failure, they found a higher prevalence of peptic ulceration in cases of anoxic cor pulmonale (10 out of 24) than in other cases of heart-failure (3 out of 64) A relatively high prevalence of peptic ulceration in emphysema at necropsy was also noted by Fulton (1953), Latts et al (1956), and Teare (1957)

Hurst and Stewart (1929), reviewing 151 cases of acute peptic ulcer, obtained a history of antecedent respiratory infection in 23% Many workers, dealing with large series of cases, have reported an increased prevalence of peptic ulcer and its complications in the winter months (Illingworth et al 1944, Jamieson 1947, 1955, Ivy et al 1950, Boles and Westerman 1954) It seemed therefore possible that the relatively high prevalence of peptic ulcer in fatal cases of emphysema might be attributable to the respiratory infection which is invariably present in these cases

To determine the significance of chronic bronchitis and acute respiratory infections in the ætiology of peptic ulcer, we questioned and examined a consecutive series of patients admitted to hospital with either gastrointestinal hæmorrhage or perforation A series of matched controls, admitted to hospital because of an acute surgical emergency, were similarly examined In addition we also attempted to assess other ætiological factors, including aspirin, alcohol, tobacco, mental stress, and certain drugs That aspirin was an important cause of gastric and duodenal hæmorrhage had been suggested by the work of Douthwaite (1938, 1954), Douthwaite and Lintott (1938), and Muir and Cossar (1955) This view, however,

TABLE I—AGE AND SEX DISTRIBUTION

—	Total	Males			Females		
		Under 45	45–64	Over 65	Under 45	45–64	Over 65
Hæmorrhage	100	13	36	13	4	19	15
Perforation	29	10	9	8	1	0	1

was challenged by the work of Paul (1943) and Wolf and Wolff (1943)

Material and Method

During the period December, 1956, to July, 1957, inclusive, 119 patients with acute gastric or duodenal hæmorrhage and 35 patients with acute gastric or duodenal perforation were admitted to the City General Hospital, Sheffield

Each patient was questioned by one of us as to symptoms of gastric disorder, chronic bronchitis, and acute respiratory infection starting within four weeks of admission to hospital, and then examined Each patient was also questioned about his consumption of aspirin, sulphonamides, oral antibiotics, alcohol, cortisone and adrenocorticotrophic hormone, phenylbutazone, and other medicines and tablets during the two weeks preceding hospital admission, and about any special strain or worry within four weeks This information, together with the clinical findings and the results of any investigations, which included radiography of the chest and stomach and, if necessary, gastroscopy, was recorded on a specially prepared form

TABLE II—CAUSES OF HÆMORRHAGE 100 CASES

—	*Males*	*Females*	Both sexes	Deaths
Peptic ulcer				
All cases	59	36	95	3
Acute	14	13	27	0
Chronic gastric	11	8	19	1
Chronic duodenopyloric	31	10	41	1
Chronic—site unknown	1	0	1	1
Hiatus hernia, œsophageal	0	4	4	0
Pyloric stenosis	2	1	3	0
Cancer of stomach	2	1	3	2
Œsophageal varices	0	0	0	0
Mucosal tear	1	1	2	0
Diffuse ooze	0	0	0	0
Total	62	38	100	5

Associated diseases hepatic cirrhosis, 4 cases, nephritis/uræmia, 1 case, cerebral thrombosis, 3 cases, lung cancer, 1 case, heart-failure, 1 case, tabetic crisis, 1 case

A control series of patients were also questioned and examined in a similar manner by the same observer, and the results recorded on the questionnaire These controls were patients admitted to hospital because of a confirmed non-thoracic surgical emergency or accident Gynæcological and maternity cases, together with patients who had symptoms of peptic ulcer, were, however, excluded Each case of hæmorrhage or perforation was matched against a control by selecting from the list of controls the first patient of the same sex, and within the same five-year age-group, who was admitted to hospital within the same two-week period

A matched control could not be found for 19 cases of hæmorrhage and 6 cases of perforation In all, 100 cases of hæmorrhage and 29 cases of perforation are analysed together with a similar number of matched controls Their age and sex distribution are set out in table I (those for the controls were similar), and the causes of bleeding and perforation in tables II and III

TABLE III—CAUSES OF PERFORATION 29 CASES OF PEPTIC ULCER

—	Males	Females	Both sexes	Deaths
Acute gastric or duodenal	6	0	6	0
Chronic gastric	2	0	2	1
Chronic duodenopyloric	19	2	21	1
Total	27	2	29	2

It will be seen from table II that in 95 of the 100 cases the cause of hæmorrhage was peptic ulceration, which in 27 cases was thought to be acute It is unlikely, however, that this latter figure is accurate as the distinction between an acute and chronic ulcer proved to be exceedingly difficult In 3 cases the hæmorrhage was from a cancer of the stomach, and in 2 patients, 1 of whom had a tabetic crisis, it was thought to come from a mucosal tear caused by excessive vomiting—a little-known but not uncommon cause described by Decker et al (1953) In each of the 4 cases of hepatic cirrhosis there was definite evidence of peptic ulceration of the stomach and in no instance was the bleeding from œsophageal varices

TABLE IV—PREVALENCE OF CHRONIC BRONCHITIS AND ACUTE RESPIRATORY INFECTIONS IN ALL CASES OF HÆMORRHAGE AND PERFORATION

—	*Males*		*Females*		*Both sexes*	
	Series	Controls	Series	Controls	Series	Controls
No of patients questioned	89	89	40	40	129	129
Acute respiratory infection (onset within 4 weeks)						
Total	35	29	18	13	53	42
Cold/sore throat	26	19	16	8	42	27
Cough and wheeze-acute bronchitis	9	10	2	5	11	15
Pneumonia	0	0	0	0	0	0
Chronic bronchitis/emphysema without heart-failure	14	24	3	5	17	29
Chronic bronchitis/emphysema with anoxic heart-failure	2	0	0	0	2	0

There were 5 deaths among the cases of hæmorrhage, which in 2 came from a gastric carcinoma A 3rd patient died from heart-failure due to anoxic pulmonary emphysema following emergency gastrectomy for recurrent bleeding, and a 4th patient died from cancer of the lung 18 patients were treated by emergency surgery, with 1 death

Of 29 patients with perforation, 27 were male and 2 female In 6 cases the ulcer was acute and in the duodenopyloric region, in 2 it was chronic and gastric, and in 21 chronic and duodenopyloric 27 patients were treated by simple surgical suture, and 1 by emergency gastrectomy There were 2 fatalities, both in men aged over 75

Acute Respiratory Infection and Chronic Bronchitis

The prevalence of acute respiratory infection and of chronic bronchitis in 129 cases of hæmatemesis or perforation is compared with the matched control series in table IV The prevalence of acute upper respiratory infection (53 out of 129) was not significantly higher than in the control series (42 out of 129), and the prevalence of chronic bronchitis, which was defined as chronic cough with wheeze or dyspnœa not due to heart-disease or other causes, was slightly higher in the controls Both in ulcer cases and in controls, chronic bronchitis was encountered more frequently in men than in women, and

TABLE V—PREVALENCE OF CHRONIC BRONCHITIS AND ACUTE RESPIRATORY INFECTIONS ACUTE ULCER AND OTHER CASES COMPARED

—	Acute ulcer	Controls	Other cases	Controls
No of patients questioned	33	33	96	96
Acute respiratory infection	13	12	40	30
Chronic/bronchitis emphysema	8	4	11	25

examine their patients, to Dr F Avery Jones and Dr Richard Doll for advice in planning the investigation, and to Miss Barbara White for statistical help

REFERENCES

Boles, R S, Westerman, M P (1954) *J Amer med Ass* 156, 1379
Decker, J P, Zamchek, N, Mallory G K (1953) *New Engl J Med* 249, 957
Douthwaite, A H (1938) *Brit med J* i, 1143
— (1954) *Lancet*, ii, 917
— Lintott, G A M (1938) *ibid* ii, 1222
Flint, F J, Warrack, A J N (1958) *ibid* ii, 178
Fulton, R M (1953) *Quart J Med* 22, 43
Hurst, A F, Stewart, M J (1929) Gastric and Duodenal Ulcer, p 89 London
Illingworth, C F W, Scott, L D W, Jamieson, R A (1944) *Brit med J* ii, 617, 655
Ivy, A C, Grossman, M I, Bachrach, W H (1950) Peptic Ulcer London
Jamieson, R A (1947) *Brit med J* ii, 289
— (1955) *ibid* ii, 227
Latts, E M, Cummins, J F, Zieve, L (1956) *Arch intern Med* 97, 576
Muir, A, Cossar, I A (1955) *Brit med J* ii, 7
Paul, W D (1943) *J Iowa St med Soc* 33, 155
Teare, D (1957) cited by Avery Jones, F *Brit med J* i, 719
Wolf, S, Wolff, H G (1943) Human Gastric Function London

ANÆSTHESIA FOR ŒSOPHAGEAL ATRESIA

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Atresia of the œsophagus has been recognised for a long time, but the first successful attempt at anastomosis was made only sixteen years ago At the Hospital for Sick Children, Great Ormond Street, between October, 1953, and November, 1956, there were 54 cases, and 30 of the infants are still living

The incidence is hard to determine Fairlie (1954) reviewed the cases occurring over five years in Glasgow and obtained a figure of approximately 1 in 5000 births, but the estimate of Belsey (1950) was 1 in 800

Diagnosis

Early diagnosis, by the correct method, is of great importance Atresia of the œsophagus should be suspected in any newborn child in whom an excess of mucus and saliva persists in the mouth and pharynx If feeds have been attempted, there will be a history of cyanotic attacks and choking

Contrast material, of any kind, should never be used to establish the diagnosis, because of the risk of spreading it through the respiratory tract, adding to the mucus (and sometimes milk) already in the trachea and bronchi and thus causing respiratory obstruction An example of this is seen in the figure Of the 54 cases at this hospital 23 had been given contrast media before admission

To confirm the diagnosis, all that is necessary is to pass a soft rubber catheter through the mouth If the catheter is held up less than 4 inches from the gums, and if stomach contents cannot be withdrawn, atresia of the œsophagus is probably present

Types of Œsophageal Atresia

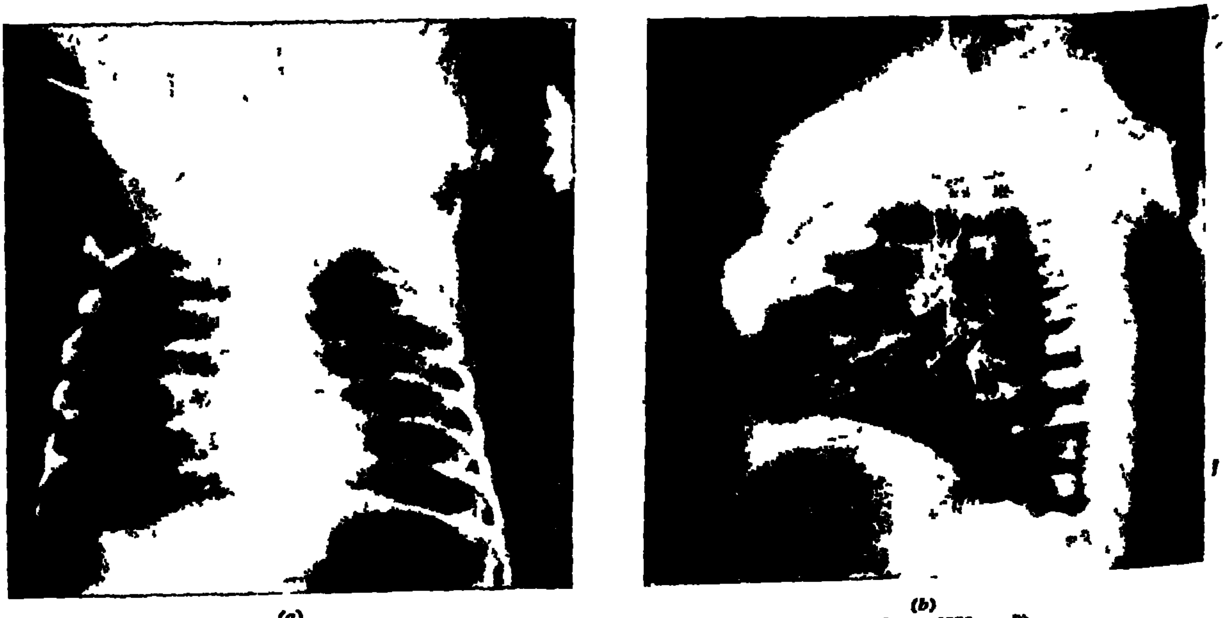
According to Waterston (1954) there are two main types, and three rare types

Main Types
- (*a*) Atresia with tracheo-œsophageal fistula into the lower segment of the œsophagus (90% of the cases)
- (*b*) Atresia without fistula (9% of the cases)

Rare Types
- (*a*) Atresia with tracheo-œsophageal fistula into both lower and upper segments of œsophagus
- (*b*) *Atresia with tracheo-œsophageal fistula into the upper segment of œsophagus*
- (*c*) Fistula without atresia

Association with Other Abnormalities

Œsophageal atresia is often associated with other congenital abnormalities, some of which may be incompatible with life for more than a few days In our series the commonest lesion was congenital heart-disease, which cannot always be diagnosed before operation These babies may appear normal in every way, with good colour, good tone, and normal heart sounds, yet at necropsy a grossly abnormal heart may be found Thus in case 39 the child died unexpectedly at the end of operation and was found to have transposition of the great vessels, infantile coarctation of the aorta, and ventricular and atrial septal defects, and there were several other cases in which heart-disease was detected


(*a*) (*b*)
(*a*) Before and (*b*) after coughing following instillation of iodised oil (ref *Anæsthesia*, 1958, no 2)

only at postmortem examination or when the patient was seen again later Furthermore, many of these cases have conditions such as rectal atresia or cleft palate, and in our series there have been infants with mongolism, hydrocephalus, agenesis of kidney, agenesis of lung, mucocolpos, and hæmangioma of liver

Of our 19 cases in which there were other major congenital defects, 14 died (tables I and II), whereas in the 35 uncomplicated cases there were only 10 deaths Thus the survival-rate was about 25% in the first group compared with about 70% in the second

Treatment

On admission to hospital the child's general condition is assessed, and the diagnosis is confirmed radiologically by passing a radio-opaque catheter into the upper pouch of the œsophagus The condition of the lungs can be seen in the same X-ray There is always collapse of the right upper lobe, and there may be patches of collapse throughout both lungs Often intercostal retraction is present, and breathing may be further embarrassed because of distension of the stomach by air sucked in through the fistula If the fistula is valvular, the stomach and intestines will overdistend with air, in which case operation is extremely urgent If the stomach is not distended, operation should be delayed for a few hours in order to

(i) Commence antibiotic treatment
(ii) Clear the air-passages as much as possible
(iii) Obtain compatible blood

Drainage of the trachea and bronchi is helped by a head-down tilt Only a soft rubber catheter should be used to suck out the pharynx and upper pouch, although the wall of the pouch is in fact hypertrophied and therefore difficult to perforate

TABLE II—MORTALITY IN RELATION TO OTHER ABNORMALITIES

Classification	No of cases	No of deaths	Mortality %
Tracheo-œsophageal fistula only or complicated by minor congenital abnormalities	31	9	29
Premature infants with tracheo-œsophageal fistula only or complicated by minor congenital abnormalities	4	1	25
Tracheo-œsophageal fistula complicated by major congenital abnormalities	13	8	61 5
Premature infants with tracheo-œsophageal fistula complicated by major congenital abnormalities	6	6	100
Total	54	24	44 4

TABLE I—SUMMARY OF CASES

Case	Age (days)	Birth-weight (lb oz)		Radio-opaque medium	Other congenital abnormalities	Relaxant	Immediate postoperative respiratory difficulty	Result
1	1			L		T	+ − +	Died
2	1	5	7	L		T	+ + −	Died
3	1			L		None	None	Survived
4	2	4	0	L	Rectal atresia	T	+ +	Died 5 days later, after gastrostomy
5	4	8	10	L		T	None	Survived
6	6	5	12	L	Right-sided aortic arch	T	None	Survived
7	4	3	14	D	Right-sided aortic arch	T	+ − +	Died
8	2	3	12	None	Rectal atresia, one kidney absent, hydronephrosis	None	Collapsed	Died
9	4	6	12	None	None	T	None	Survived
10	4	9	0	None	None	None	None	Survived
11	1	5	10	B	Atrial and ventricular septal defects		Collapsed	Died
12	5	5	14	L	Right-sided aortic arch		− − −	Died
13	63	6	4	B	None	T	− + +	Died
14	7	8	0	None	Hydrocephalus	T	None	Died 2 days later
15	3	5	10	L	Fallot's tetralogy	T	None	Survived
16	1	8	1	None	None	None	Tension pneumothorax	Survived
17	4	7	6	None	None	T	None	Survived
18	2	7	0	L	None	T	None	Survived
19	1	3	4	None	Atrial septal defect	G	+ − +	Died
20	3	4	12	None	None	None	None	Survived
21	2	7	9	None	Pulmonary stenosis	G	None	Survived
22	2	3	9	L	Mongolism, ventric septal defect, persist. duct arterios	None	− − +	Died
23	3	6	10	L	None	None	None	Died
24	1			None	None	None	None	Died
25	3	6	4	L	None	S	None	Survived
26	3	4	8	None	None	S	None	Survived
27	6	7	9	None	None	S	None	Survived
28	1	6	3	None	None	S	None	Survived
29	4	7	1	None	Ectopic anus, sclerema	S		Died
30	2	6	1	L	Large liver tumour	S	None	Died
31	2			None	None	S	None	Survived
32	1	5	10	None	Rectal atresia mucocolpos	S	None	Died 6 weeks later, after 2nd operation
33	2	7	8	L	None	S	None	Survived
34	5	4	12	None	None	S	None	Survived
35	1	5	13	None	None	None	None	Survived
36	3	6	0	None	Rectal atresia	S	None	Survived
37	1	6	2	None	Atrial and ventricular septal defects	S	Collapsed	Died
38	5	7	0	None	Agenesis of left lung heart-disease	T	None	Died 6 weeks later, after 2nd operation
39	1	7	0	None	Great vessels transposed aorta coarctated, tricuspid atresia, cleft palate &c.	S	Collapsed	Died
40	2	3	13	None	Rectal atresia	S	None	Died 2 months later
41	2	6	2	L	None	S	Immediate postoperative collapse responded to treatment	Survived
42	10	7	4	L	None	T	None	Survived
43	2	6	8	None	None	S	None	Died
44	2	6	6	None	None	T	− −	Survived
45	7 hr	6	10	L	Ectopic anus, cleft palate	S	None	Survived
46	1	6	14	None	None	S	None	Survived
47	3	6	12	D	Heart-disease	S	None	Died later
48	1	6	0	None	None	S	None	Survived
49	4	8	0	None	None	S	None	Survived
50	5	5	0	None	Heart disease, sclerema			Died *
51	2	6	14	None	None	None	None	Survived
52	3	6	9	None	None	S	None	Survived
53	3	7	7	L	Second tracheo-œsophageal fistula	S	− − +	Died later
54	1	5	11	L	Rectal atresia	T	− −	Survived

L = 'Lipiodol' D = 'Dionosil' B = barium T = tubocurarine S = suxamethonium. G = gallamine.
* In this case the operation was confined to tracheostomy and gastrostomy

Preoperative intravenous fluid is unnecessary, for the child is seldom dehydrated, but an intravenous drip (5% dextrose, preferably into the left arm) should be set up in the operating-theatre to facilitate administration of drugs, or blood, if required

Atropine 0 3 mg is given intramuscularly half an hour before operation This stops the flow of saliva, which may be inhaled, and also prevents the vagal slowing of the heart which may result from local surgical stimulation But if the secretions are viscid, atropine, by increasing their viscosity, may cause further obstruction to breathing, and is better avoided, though it may be given during the operation if the heart-rate slows unduly

The Anæsthetic Plan

Anæsthesia for œsophageal atresia must provide for a right thoracotomy and transpleural approach to the mediastinum, where, with the right lung collapsed, the upper and lower pouches of the œsophagus are identified, dissected out, and the two ends anastomosed Diathermy is used

To ensure oxygenation, and to permit removal of secretion from trachea and bronchi during operation, intubation of the trachea is necessary, and this is one of the most important details of the anæsthetic procedure

Surgery is possible after endotracheal intubation and nitrous-oxide/oxygen anæsthesia (10 cases, see table II) However, as the breathing of newborn infants is more diaphragmatic and abdominal than intercostal, each breath will draw the lower pouch down and away from the upper pouch, similarly swallowing will cause the upper pouch to move upwards and away from the lower pouch This constant movement and jerking of the diaphragm makes anastomosis difficult for the surgeon, who is already working in a small field A sound anastomosis is very important, because postoperative leaking causes mediastinitis

Perfect conditions may be obtained by the use of muscle relaxants Oxygenation is effected by controlled inflation of the left lung and the part of the right lung which is not completely collapsed by retractors Thus breathing may be modified to avoid interference with the operation

Choice of Relaxant

For some time at this hospital *d*-tubocurarine chloride was used, but recently we have found that with suxamethonium ('Scoline') there are fewer cases of respiratory difficulty or complications, immediate or delayed Of the 23 cases given suxamethonium, only 1 (case no 53) showed postoperative respiratory difficulty, and this was traced to a second tracheo-œsophageal fistula, whereas of the 18 cases given tubocurarine or gallamine 8 had postoperative respiratory trouble (table III) Stead (1955) showed that the newborn infant is far more resistant to depolarising agents than the adult, though the pseudo-cholinesterase level may be as low as 40%, and also that the inverse relation between sensitivity to depolarising agents and to competitive agents holds true Thus the newborn is very sensitive to tubocurarine, reacting in the same way as a myasthenic patient

The advantage of suxamethonium is that there is no danger of the patient remaining curarised after the operation The disadvantage is that its effect lasts so short a time that repeated injections must be made (Each injection tends to have a longer effect than the one before) With tubocurarine, on the other hand, no matter how small the dose, it is scarcely possible to ensure that the patient is not still curarised at the end of the operation, for reversal of its action by neostigmine does not seem to be reliable (Rees 1950) Unlike those of the adult, the limb movements of a partially curarised infant may appear vigorous, but they differ from the normal movements by their jerkiness

TABLE III—RELATION OF POSTOPERATIVE RESPIRATORY DIFFICULTY TO THE USE OF RELAXANTS

Relaxant used	No of cases	Cases showing postoperative respiratory difficulty	Percentage of cases
		Number	Percentage
Tubocurarine or gallamine	18	8	44
Suxamethonium	23	1	4
Unrecorded	2	1	
None	10	1	10

Anæsthetic Management

The first step in anæsthetising these patients is to ensure that they are well oxygenated Newborn infants have a high hæmoglobin—usually above 100%—which means that they will show cyanosis quickly

Oxygen alone is given for 2–3 minutes, after which laryngoscopy is carefully carried out on the conscious patient (M H and P M H) The contents of the pharynx and upper pouch of the œsophagus (secretions, milk, iodised oil) are removed by suction The fine gum elastic catheter used for this purpose may also be passed through the cords, sucking trachea and bronchi clear The smallest-size endotracheal tube is passed into the trachea As the average length of the trachea in the newborn is 4 cm, care must be taken not to pass the tube further than this through the cords A Cobb's connection is used so that suction of the trachea and bronchi is possible during operation

An alternative method of induction (R W C) is to give intravenous suxamethonium after a few breaths of oxygen, followed by laryngoscopy and careful suction of pharynx and trachea Intubation and suction are made easier by giving a relaxant first, but it is probably wiser to view the larynx before suxamethonium is injected Unless one has reasonable confidence in the intubation, the first method should be used, because it is difficult to inflate the lungs of these small patients with no tube in situ

Anæsthesia is maintained with equal amounts of oxygen and nitrous oxide, and intravenous suxamethonium is given intermittently The initial dose is 0 5 mg per lb body-weight and the length of time necessary to eliminate this is noted If it is short, as is usual, the next injection is 1 0 mg per lb, and this is repeated, as required, until the time between injections is found to be lengthening The dose is then decreased to 0 5 mg per lb or even less If possible the total dose should not exceed 50 mg The suxamethonium is diluted, with sterile water, to a strength of 5 mg per ml

If the intravenous infusion is not satisfactory, suxamethonium may be given in the same dosage intramuscularly—preferably with hyaluronidase, to ensure that all the drug is absorbed before the end of the operation Each injection by this route takes effect within 2 minutes and lasts for about 10 minutes

After induction, a nasal catheter (size 5), containing a fine polythene tube (size 2), is passed through the nose to the limit of the upper pouch This helps the surgeon to identify the pouch, and, when this is opened, the polythene tube is anchored and the rubber catheter removed Just before the final anastomosing stitches are inserted, the polythene tube is passed through the lower pouch into the stomach, where it remains for postoperative feeding purposes

Respirations are controlled throughout the operation, using a high flow of gases (3 litres oxygen and 3 litres nitrous oxide) with, or without (M H), a 12 oz or 8 oz Waters' canister containing soda-lime The pressure needed to inflate the lungs of the newborn is more than that required for an older child, partly because the smaller endotracheal tube has a higher resistance Elimination of carbon dioxide is assisted by the high flow of gases, by adequately controlled respiration, and by the use of the canister—the high flow of gases being the most important factor

The average newborn child requires about 25 c cm oxygen per minute (Smith 1951), and as the tidal air is approximately 20 c cm (Cross 1949), a rapid respiratory rate is needed Rates of up to 40 per minute are usual Rates exceeding this may diminish tidal exchange and embarrass venous return to the heart

With this technique the patient, at the end of operation, will be awake and crying, with a good colour, good muscle tone, and good movements of the chest wall

Difficulties

The first difficulty encountered during anæsthesia may be distension of the stomach with anæsthetic gases passing through the fistula, particularly if this is large (If the endotracheal tube itself passes through the fistula into the lower pouch, the stomach will be inflated but not the lungs) This difficulty can usually be overcome by altering the position of the tube, but, if not, the surgeon must be asked to close the fistula as quickly as possible Meanwhile, a hand pressed gently over the stomach will prevent overdistension, and permit inflation of the lungs When the fistula has been closed, the stomach may be emptied of gases by passing a catheter through the lower pouch

The pressure of the assistant's retractor may cause anxiety, for the trachea and bronchi are soft and easily compressed If a good colour can be maintained by inflation of the left lung, pressure on the right main bronchus does not matter, but usually this is not so, and the pressure of the retractor must be released Pressure over the pericardium can slow the heart and should be avoided

One of the main difficulties is estimation of the degree of shock The newborn infant may be apparently well only a short time before it is obviously moribund The various stages of shock are not easily recognisable as they are in the adult Assessment of the patient's condition is helped by strapping a small stethoscope over the heart. As in the fœtus, the onset of shock is indicated by slowing of the heart-rate The radial pulse disappears early, because of vasoconstriction in the limbs If any radial pulse can be felt, the condition is satisfactory, but its absence does not imply the degree of shock which would be expected in an adult undergoing thoracotomy

The length of the operation is important, for if the chest is open for more than 1¹/₂ hours the child's general condition will usually give rise to anxiety The use of relaxants, as described above, allows the surgeon to work under ideal conditions, using diathermy, and thus decreases operating-time

Usually, little blood is lost and its replacement may not be necessary However, as the blood-volume of the newborn is 40 ml per lb (making a total of only 200–300 ml), even a small loss must be replaced if shock is to be prevented A deficit of more than a tenth of the total volume should not be permitted, for infants tolerate blood-loss badly, and later replacement is not always successful If the loss cannot be measured, 10 ml of blood per lb body-weight may safely be given without overloading the circulation, but it is our practice to weigh the swabs and to replace the blood through a finely graduated drip chamber

The temperature of these patients always falls during operation, and to a certain extent this is a protective mechanism Temperatures may be as low as 86°F, though more often the reading is 88–89°F The patient should not be actively warmed, but further heat loss should be guarded against He will gradually regain the normal temperature, sometimes taking two or three days to do so, and the quicker he regains it the better will be his general condition This is still a controversial subject

When the operation is complete, the right lung is gently re-expanded If a thoracic drain is used, it is attached to an underwater seal as soon as the chest is closed The pharynx is carefully sucked out, and when the respirations are adequate, the endotracheal tube is removed

Postoperative Management

Constant skilled nursing attention, together with almost constant medical supervision, is essential during the first few postoperative days The airway must be kept clear of secretions, by repeated suction of mouth and pharynx The infant is nursed flat because of the danger of reflux gastric secretions reaching the site of the anastomosis when in the head-down position The secretions may be so viscid that suction is difficult 'Alevaire', a detergent, lowers the surface tension of the thick mucus, thus facilitating suction it is given by passing the oxygen over a solution of alevaire on its way to the box in which the infant is nursed Pulmonary collapse due to blocking of the bronchi by secretion can thus be prevented

This problem is complicated by abnormalities in the trachea itself There is a valve-like fold of mucous membrane lying over the fistula opening in the posterior wall of the trachea, as described by Franklin and Graham (1953) This fold may become œdematous after operation, causing further restriction of the airway Also, because of abnormality of its cartilaginous rings, the trachea may tend to collapse on inspiration If the airway is restricted in this way, the endotracheal tube may have to be replaced

As a routine, the chest is radiographed on the first postoperative day

Conclusions

What conclusions may be drawn, and what policy formulated, from this small and unselected series of 54 cases ?

Early recognition of the condition and early transfer to a unit accustomed to such cases, are major conditions of success Additional abnormalities diminish the likelihood of saving the child

Where the anæsthetist can tip the balance towards success seems to be in his choice of a relaxant technique giving ideal conditions to the surgeon and therefore shortening the operating-time Of the relaxants, succinylcholine is preferable to tubocurarine or gallamine, because its use is much less often followed by postoperative difficulties in respiration Success depends not only on the main lines of policy but also on attention to the minutiæ of technique

We gratefully acknowledge permission to describe this series of cases, all of which were treated by the surgical consultant staff at the Hospital for Sick Children, Great Ormond Street To all our anæsthetic colleagues, we also express our sincere thanks for their kindly cooperation

REFERENCES

Belsey, R H R , Donnison, C P (1950) *Brit med J* ii, 324
Cross, K W (1949) *J Physiol* 109, 459
Fairlie, H (1954) *Glasg med J* 35, 145
Franklin, R H , Graham, A J P (1953) *Thorax*, 8, 102
Rees, J G (1950) *Brit med J* ii, 1419
Smith, C A (1951) The Physiology of the New Born Infant, p 155
Stead, A L (1955) *Brit J Anæsth* 27, 124
Waterston, J (1954) Recent Advances in Pædiatrics, p 151 London

STAPHYLOCOCCAL INFECTION IN MOTHERS AND INFANTS

MATERNAL BREAST ABSCESSES AND ANTECEDENT NEONATAL SEPSIS

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ANTIBIOTIC-RESISTANT strains of staphylococci are now firmly entrenched and widely distributed in New Zealand Most epidemics and sporadic infections have been caused by a staphylococcus of relatively high drug resistance, of the phage-type 80/81, the type of organism closely studied by Rountree (1955) in Australian maternity infections One serious maternity hospital epidemic with a high mortality-rate has occurred (Beaven and Burry 1956, Douglas and Knights 1956) and less serious and smaller epidemics have arisen throughout the country Early in 1957 the number of patients admitted to a general hospital for treatment of breast abscesses during lactation reached serious proportions (15 cases in four months), whereas, in the preceding fifteen years (annual birth-rate of 1500 to 2300) only 4 to 6 cases were admitted each year When it was found that several of these women had been delivered in one maternity hospital (Hospital B), an investigation was instituted, and techniques were revised to control the epidemic and prevent further introduction and spread of infection

The relationship of maternal breast abscess, neonatal sepsis, and staphylococcal carriage in staff, mothers, and infants was also studied

A further outbreak in a smaller institution was also investigated The results of these investigations and the methods used to control the outbreaks are reported below

Material and Methods

Maternal Breast Abscesses

37 cases of maternal breast abscess, developing in the weeks following childbirth, are known to have followed confinement in maternity homes in this city in the past twelve months 31 of these required hospital admission for incision and drainage, and in 32 cases bacteriological investigations were carried out Information was obtained concerning the length of the time between delivery and onset, relationship to lactation, cracked nipples, infection in the infant, and place of delivery In 12 cases, additional information was available from the mother's nose and/or breast milk, and the infant's nose and/or lesion, as well as from the abscess Breast milk from 33 women (11 with abscesses and 22 normal), was examined for staphylococci

Buildings

Bacteriological investigations were carried out in Hospital B, a maternity unit of 44 beds, attached to Hospital A, an acute general hospital which serves a population of about 100,000, and a subsidiary investigation was carried out in a smaller " open " maternity home (Hospital C) of 20 beds where women are attended by their own practitioners

Hospital B is a three-storey concrete building, adjacent to Hospital A but with a separate staff It is of modern construction and is designed for efficient cleaning and dust control The patients are accommodated in single, double, and four-bed wards, and there are two large air-conditioned nurseries, an air-conditioned room for premature infants, and an isolation-room for the segregation of infected infants

Hospital C is a single-storey brick building which was not originally designed for maternity work and is older than Hospital B It contains 4 four-bed wards, 2 single, and 1 double room, and 2 rather small nurseries Because of the *difference in the design and state of the fabric of the two* buildings, efficient cleaning is more difficult in Hospital C than in Hospital B

In both institutions, dust and air samples were collected and examined for pathogenic staphylococci Dust was collected on moistened, serum-impregnated, cotton-wool swabs, and air was cultured by means of the slit-sampler, at the rate of 5 c ft. of air to one blood-agar plate in a five-minute period

Neonatal Sepsis

In Hospital B, in the first four months of 1957, while not all " sticky eyes " or minor skin lesions were swabbed, bacteriological data were available on septic skin lesions from 26 of the 232 infants born alive in that period After the introduction of special control measures in April, every suspected staphylococcal lesion in the infants was swabbed for bacteriological examination In the six months May to October, 1957, 52 (13%) of the 402 infants born alive were swabbed These included 25 skin lesions and 21 cases of " sticky eye " In unselected cases, swabs were taken from the nose and umbilicus of the infant, as well as from the lesion, and also samples from the mother's breast milk

Nasal Carriage of Staphylococci

The nasal carriage-rate was investigated in nursing and other staff of Hospital B in January, May, and September, and in Hospital C in September

With the help of three senior students (Burkinshaw, Hamer, and Swier 1957), 113 consecutive mother and infant pairs were swabbed The mothers were swabbed within twenty-four hours of admission, and again on the tenth day of the puerperium, and the infants on the fourth and tenth day of life 19 mothers in Hospital C and 22 infants in that home on a given day were swabbed

Bacteriology

Specimens of exudate, or nasal swabs, were collected on sterile serum-impregnated swabs, and primary culture was made on to blood-agar plates Colonies of staphylococci were subcultured into nutrient broth and tested for coagulase activity by the method of Fisk Strains showing coagulase activity, which was taken as an indication of pathogenicity, were tested for antibiotic sensitivity by a disc method Six-hour nutrient-broth cultures were subcultured on to nutrient-agar plates in such a way that a peripheral zone of the plate, 2 cm. wide, was sown with the test organism Discs impregnated with various antibiotics (penicillin 3 units, streptomycin 66 µg , chlortetracycline (aureomycin) 20 µg , chloramphenicol 20 µg , oxytetracycline (terramycin) 20 µg per ml) were placed along the inner edge of the cultured zone Each disc was controlled by making radiating streak cultures of the Oxford strain of staphylococcus from the centre of the plate to each disc. A zone of inhibition of the test organism equal to at least half that shown by the control staphylococcus was taken as indicating that the test organism was sensitive to the antibiotic concerned

Methods of Control

When the "epidemic strain" of staphylococcus had been determined the following measures were taken to control its further spread and to attempt its elimination from the hospital

Nasal swabs of all Hospital B staff (nursing, medical, cleaning, and clerical) were taken and carriers of the "epidemic strain" were put off duty and treated with local application of 1% chlorhexidine ('Hibitane') cream or neomycin-bacitracin ointment until free of contamination.

Any infant with clinical sepsis was isolated, either by "rooming in" with the mother or in the isolation nursery Barrier nursing was applied and bacteriological investigations were made. Gowns and masks were worn in the nurseries at all times, and hexachlorophene (G11) soap and 1% chlorhexidine hand-cream were used routinely before and after infant handling Disposable towels continued in use The bathing of babies was discontinued, they were oiled after birth and cot-treated thereafter until discharge on the twelfth to fourteenth day

The heating and ventilating plant was overhauled One plant, which was removing dusty air from a nursery and returning it to the premature nursery, was converted to the "plenum" system for both rooms Blinds and curtains in the nurseries are being replaced by external blinds

TABLE I—PHAGE-TYPES OF STAPHYLOCOCCI ISOLATED FROM 33 MATERNAL BREAST ABSCESSES

Phage	Antibiotic sensitivities* Su	P	S	A	C	T	No of strains	No of cases
52 52A 80 81	—	—	=	—	—	—	1	24
80 81	—	—	≡	—	—	—	20	
	—	—	—	—	—	—	2	
	—	—	—	—	—	—	1	
3B 3C 55	≡	—	—	—	—	—	1	2
	—	—	—	—	—	—	1	
47—	—	—	—	—	—	—	1	1
53 54 75 77—	—	—	—	—	—	—	1	1
Unknown		—	—	—	—	—	1	5
		—	—	—	—	—	1	
		—	—	=	—	—	1	
	Coagulase-negative						1	
	Not tested						1	

* Sulphonamides penicillin streptomycin chlortetracycline (aureomycin), chloramphenicol oxytetracycline (terramycin)
— = sensitive, — = resistant, = = moderately sensitive.

All bedding was sent to the laundry when mother and infant were discharged Cotton articles were washed and steam-pressed, which effectively sterilised them, and blankets were washed and treated with 'Lissapol' and 'Cirrasol' (Blowers and Wallace 1955)

The midwife admitting a mother asked for a family or personal history of recent sepsis A nursery record of all infections was started, and measures were taken to avoid overcrowding as far as was possible in a public institution which has to admit obstetric emergencies on request.

The umbilicus of each infant was dressed daily with alcohol The use of a binder (until the cord separated) was continued, since the results of swabbing were such that no change in technique was considered necessary Circumcisions were discontinued while there was any risk of nursery infection The routine instillation of sulphacetamide drops into the eyes of each newborn infant was stopped, and instead the eyelids were wiped with sterile saline-soaked cotton-wool

TABLE II—DISTRIBUTION OF BREAST ABSCESS CASES AND THEIR PHAGE-TYPES

—	No from Hospital B	Hospital C	Other homes	Total
No of cases swabbed	15	12	6	33
No coagulase-positive	15	11	6	32
No of 80 81 strains	10	9	5	24
No of 3B 3C 55 strains	1	0	1	2

Methods of Treatment

In addition to isolation, each infected infant received local treatment for the lesion

10% sulphacetamide was given for conjunctivitis and 1% gentian violet for pustules, if the infant remained well Systemic antibiotics, as indicated by the antibiotic-sensitivity tests, were reserved for cases of severe paronychia, furuncles, or abscesses In most cases chloramphenicol was used and no reactions were observed Any child who was toxic was transferred to the children's ward of the main hospital Only 1 transfer was necessary in over 50 cases in eight months Any lesion containing pus was incised.

Results

Maternal Breast Abscesses

Coagulase-positive staphylococci were obtained from 31 of 32 cases investigated 24 strains were identified as phage-type 80,81, and 21 of these had a characteristic antibiotic-sensitivity pattern (table I)

Time of onset—23 of the 33 abscesses developed between two and four weeks after confinement, 2 as late as twelve and fourteen weeks No relationship in time to any significant change or event in lactation has been discovered

Mode of onset—27 patients out of 29 gave a history of cracked nipples in the mother or infection in the infant, or both In the 29 patients interrogated, the abscess developed after an infection in the infant on 25 occasions, and after a cracked nipple in 14 In 11 there had been both an infection and a cracked nipple Many of these infants were unfortunately not available for detailed bacteriological investigation by the time the mother was seen in hospital 9 mothers are known to have had septic skin lesions which developed after confinement and before the abscess

Antibiotics had been given to 22 patients, but failed to cure the lesion and in no case did antibiotics cure once a mass had formed

16 patients required incision on two or more occasions and both breasts were affected in 5 The stay in hospital varied from three days to over six weeks (including readmissions), the majority of patients needed one to three weeks' hospital treatment.

The source of the cases and the bacteriological findings are shown in table II The 15 patients from Hospital B had been delivered in a six months' period, giving an abscess rate of 4% of confinements 9 of the Hospital C patients were delivered in a period of four months, a rate of 5% of confinements

Table III gives the results of groups of swabs taken from the same case (the maternal nose, breast milk, infant's nose, and/or lesion) While the strain of organism isolated from the abscess was isolated from the mother's nose on only 2 out of 12 occasions, the "abscess strain" was carried by the infant in almost all the cases studied

TABLE III—COMPARISON OF STAPHYLOCOCCI OBTAINED FROM THE NOSE AND BREAST MILK OF THE MOTHER, AND THE NOSE AND LESION OF THE INFANT, WITH THOSE FROM THE MATERNAL BREAST ABSCESS

—	Maternal nose	Maternal milk	Infant's nose	Infant's lesion
No swabbed	12	11	11	12
No of coagulase-positive swabs	2	6	9	11
Same phage-type as abscess in	2	5	9	11

TABLE IV—SKIN-SEPSIS RATES IN HOSPITAL B BEFORE AND AFTER INTRODUCTION OF CONTROL MEASURES

No of	January–April		May–October	
Live births	232		402	
—	No	% live births	No	% live births
Skin lesions swabbed	26	11	25	6
Coagulase-positive swabs	23	10	15	3 5
80/81 strain	13	6	3	0 7

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No coagulase-positive staphylococci were isolated from the samples taken from the nurseries and theatres in Hospital B, although much dust and a variety of organisms were obtained from various sources. In the older institution (Hospital C), however, 9 of 43 specimens were positive, 2 being identified as type 80/81 (table VI).

Discussion

Since the description in Australia, by Rountree and Freeman (1955), of a newly identified strain of staphylococcus, the phage-type 80 or 80/81, this strain has now been identified in over 40 epidemics in many parts of the world (Shaffer 1957). Since it was first identified in New Zealand as a phage 52A variant (Battersby and Stringer 1954) and subsequently typed (weakly) as 42E/7/73 (Beaven and Burry 1956), Shaffer (1957) has shown the identity of the type 80 or 80/81 with the Canadian strain V-81, and his 42B/47C/44A/52/80/81 strain in the U.S.A. This strain appears to show a predilection for maternity homes (Markham and Shott 1958).

The presence of a particular strain of staphylococci in maternity hospitals is an interesting and as yet unsolved problem. It does appear, however, that the type 80/81 and certain other strains of staphylococcus find the environment of a maternity home particularly well suited to their propagation. It has been suggested by Rountree and Freeman (1955) and Gillespie and Alder (1957) that this strain was of exceptional virulence, but in view of the frequency with which it occurred in minor lesions and the comparative rarity of severe complications, the property of "exceptional" virulence cannot be attributed to the organism seen here.

It is now accepted (Rountree et al. 1956) that breast abscesses during lactation are almost invariably due to staphylococci acquired in the maternity home, often from an infected infant, and our survey confirms these findings. Thus the control of an epidemic of breast abscesses involves the control of neonatal infection in the maternity home. Further, since asymptomatic carriage of staphylococci seems to be almost as dangerous (both for mother and infant) as frank sepsis, nasal carriage of staphylococci by the infants is of importance. It was gratifying to find that the nasal carriage of all coagulase-positive staphylococci by the infants was reduced to under 40% by the measures described. This figure compares most favourably with those quoted by Gairdner (1954) and others.

Duncan and Walker (1942) showed that staphylococci were common in maternal milk, and they found that these organisms were derived from the infant's nose or throat (which was colonised first) and not from the mother's nose. It appeared to us that the importance of breast milk in the transmission of staphylococci had not been fully appreciated, and this view has been confirmed independently by Wysham (1957).

In a maternity home, where dust and aerial contamination is common, a woman with cracked nipples appears to be at a considerable risk regardless of the state of her infant. This may well have been the explanation of 4 of the Hospital C patients, none of whom carried staphylococci in their milk, but who, 2 or 3 at a time, had all been in one four-bed ward. Milk may be much more important as a vector in a unit such as Hospital B where cleaning is effective and dust and aerial contamination in the wards slight or absent. Under such conditions, the train of events in the production of a breast abscess may be introduction by a staff carrier, transfer to infant by hand or aerial spread, transfer from infant to infant in the nursery by hand or air, from infant to maternal milk, whence, in the presence of engorgement (of all or a part of the breast) or cracked nipples, an abscess develops.

The technique of antenatal expression of colostrum advocated by Waller (1946) is recommended to all women attending the antenatal clinic of Hospital B, and only 3 out of 24 patients with breast abscesses had practised this exercise. The benefits of this expression may not only be easier and more effective lactation but also, through improved function of the duct system of the breast, at least some degree of protection against abscess formation. The periodical examination of samples of bulk breast milk from a maternity home may be a valuable screening procedure, since, if a sample produces coagulase-positive staphylococci, a search may be made for the woman responsible. It has also been valuable to culture the milk of the patient in any case of pyrexia of unknown origin in the puerperium.

Williams (1956) described three types of neonatal sepsis: staphylococcal infections of one phage-type from a single source (such as a nurse with boils), infections due to staphylococci which are of one type but are widespread in the environment, and infections by several phage-types which are similar to those carried by the nurses. This last group he considers, is due to inadequate techniques. It seems that these are not mutually exclusive and that the first, if not rapidly controlled, would lead to the second. The experience in Hospital B corresponds closely to Williams' first group, since the sudden appearance of an epidemic of breast abscesses suggested that a new organism especially well adapted for survival in a maternity hospital had been introduced. When this possibility was examined in Hospital B, it was found that one of the nursing staff not only carried organisms of the 80/81 strain in the nose but had suffered from recurrent boils caused by the same organism, and, since McDonald and Timbury (1957) have suggested that staphylococci from subacute infections are more pathogenic than those from a healthy mucous membrane, this may explain the sudden increase in infections. The removal of this nurse from duty was the beginning of the end of this particular epidemic, and in the following six months there was only one breast abscess among the Hospital B patients, and this was due to a different phage-type.

In contrast, Hospital C, the older building, which was more difficult to clean adequately, had an outbreak of the second type with contamination of dust and air.

In Hospital B, the eradication of staff carriers of the epidemic strain, plus the introduction of new nursery techniques to reduce cross-infection, was effective in controlling the outbreak due to the 80/81 strain and also in reducing the "residual" sepsis of Williams' third group.

Most infants born in Hospital B were seen by one of us (J. A. M.) at a follow-up clinic, at the age of six to eight weeks, and, while some who had been free of infection in Hospital B had developed pustules or conjunctivitis after discharge, almost all infants appeared to clear up spontaneously by the age of two months, regardless of treatment.

During the ten months of the survey only 1 infant had to be transferred from Hospital B to the children's ward of the general hospital. This child progressed from crops of pustules to a massive subcutaneous abscess of the forearm. No case of staphylococcal pyopneumothorax was seen from Hospital B, though 9 cases (with 4 deaths) were admitted to the children's ward of the hospital during the period. These cases, which show the danger of staphylococcal complications, closely resemble those described by Beaven and Burry (1955) and Briggs (1957).

Our methods of treatment and control correspond closely with those advocated in the monograph of the

TABLE IV—SKIN-SEPSIS RATES IN HOSPITAL B BEFORE AND AFTER INTRODUCTION OF CONTROL MEASURES

No of	January–April		May–October	
Live births	232		402	
—	No	% live births	No	% live births
Skin lesions swabbed	26	11	25	6
Coagulase-positive swabs	23	10	15	3.5
80/81 strain	13	6	3	0.7

Breast milk—The "abscess strain" of staphylococcus was isolated from the breast milk in almost half the cases examined 32 samples of breast milk were also obtained from 16 mothers in Hospital B who showed no sign of infection, but whose infant carried or was infected with staphylococci 7 mothers carried the same strain in the milk as that isolated previously from the infant, thus, as in the abscess series, almost half the patients yielded infected milk In 33 cases examined in Hospital B we have not found staphylococci in the breast milk of a woman whose child had a negative nasal swab

Infant Sepsis

In the four months before the introduction of the new nursing techniques in Hospital B, at least 11% (some lesions were not swabbed) of the 232 infants born alive had staphylococcal skin lesions 13 swabs grew staphylococci of phage-type 80/81 In the six months after the application of the new techniques the proportion of infants with staphylococcal skin lesions fell to 6% of 402 live births, organisms of phage-type 80/81 being found in only 3 infants The details of the infant-sepsis rate during the two periods are set out in table IV

Table V analyses the type of lesion and the results of bacteriological examination Only 6 out of 20 "sticky eyes" and 4 out of 12 pustules produced coagulase-positive staphylococci, whereas all cases of paronychia were caused by this organism

The nose and lesion of an infant were swabbed at the same time on 11 occasions, 5 of these pairs grew coagulase-positive staphylococci from both swabs, and in 4 the identical organism was present in both nose and lesion

Umbilical sepsis—No frank examples of umbilical sepsis were encountered during the period of this study 14 umbilical swabs were examined for various reasons and when bacteriological culture was carried out it was found that in only 3 cases were coagulase-positive staphylococci present, while 3 others carried *Escherichia coli* From the remaining 8 swabs either coagulase-negative staphylococci were obtained or there was no growth

Nasal Carriage by Staff

The incidence of coagulase-positive staphylococci in the nose of staff personnel is shown in table VI The variation in numbers of Hospital B staff swabbed is due to the inclusion of cleaning and domestic staff in the latter two surveys and to the presence of a new class of trainee nurses in September

While the proportion carrying coagulase-positive staphylococci (positive carriers) varied from 22% to 48%, the proportion of penicillin-resistant staphylococci remained about 70% Similar figures were obtained from the medical staff The single carrier of type 80/81 (among the nursing staff) in September was a "persistent carrier", first identified in January as the probable source of the 80/81 strain in Hospital B nursery infections

41 of the Hospital B staff (nursing, cleaning, and domestic) were present for both the May and September surveys 20 of these were non-carriers on both occasions 11 who were positive in May had become negative by September, while only 2 non-carriers in May were positive in September 8 were positive on both occasions, 4 of them carrying the same or a closely related strain (as shown by phage-typing and sensitivity pattern) on both occasions

TABLE V—TYPE OF LESION AND BACTERIOLOGICAL RESULTS (IN A SIX-MONTH PERIOD WITH 402 LIVE BIRTHS)

—	Lesion					
	"Sticky eyes"	Skin				Total skin
		Pustules	Blisters	Scabs	Paronychia	
No swabbed	20	12	4	2	7	25
No producing coagulase-positive staphylococci	6	4	3	2	7	16
No producing coagulase-negative staphylococci	9	7	1	0	0	8
Other organisms	1	0	0	0	0	0
No growth	4	1	0	0	0	1

One pædiatrician who visited Hospital B weekly had exchanged a penicillin-sensitive strain that was untypable in May, for a highly resistant strain, phage-type 80/81 in September This was almost certainly acquired from the children's ward of the hospital, where cases of staphylococcal empyema due to the phage-type 80/81 were under his care

Nasal Carriage by Mothers and Infants

In Hospital B only 2 women of the 113 examined carried the 80/81 strain on admission, and 1 had lost it by the tenth day The overall maternal carriage rate of coagulase-positive staphylococci was 30% to 36%, but in this group the incidence of penicillin-resistant strains was half that of the nurses or infants The small group of 19 mothers in Hospital C gave a similar figure (30%) 41% of the 22 infants in Hospital C were carriers at the time

TABLE VI—NASAL CARRIAGE OF COAGULASE-POSITIVE STAPHYLOCOCCI

—	Source of swab		No of swabs	No coagulase-positive	% coagulase-positive	No penicillin resistant	% penicillin resistant	No of 80/81 strain
Hospital B	Staff (nurses only)	January	36	8	22	5	63	2
	Staff (nursing and cleaning)	May	46	22	48	15	68	4
	Staff (nursing and cleaning)	September	55	16	29	12	76	1
	Staff (medical)	May	8	3	38	2	—	0
	Staff (medical)	September	11	4	36	2	—	1
	Mothers (April, May, June)	1st day	113	34	30	16	47	2
		10th day	113	41	36	13	32	1
	Infants (April, May, June)	4th day	113	22	19	13	59	1
		10th day	113	39	34	29	74	2
Hospital C	Staff (nursing and cleaning)		21	6	22	4	19	1
	Mothers		19	6	32	1	21	0
	Infants		22	9	41	7	32	2
Hospital B	Dust and air (nurseries and theatre)		15	0	0	0	0	0
Hospital C	Dust and air (nurseries, wards, and theatre)		43	9	21	4	9	2

Australian National Health and *Medical Research Council* (Rountree et al 1956) (which contains an extensive bibliography), two points from which have been adopted here the use of 2% gentian violet in 70% alcohol for local application to pustules and the discontinuance of routine eye-drops at birth

It seems that there must be a minimum level of sepsis of the third type, since it is not practicable, nor are we convinced of the advisability of treating all nasal carriers of coagulase-positive staphylococci, as it has been suggested (Rountree and Barbour 1951) that carriage of one strain (possibly penicillin-sensitive) may protect against the acquisition of a more virulent or more resistant strain, and it became apparent, with the decrease in amount of sepsis in Hospital B after the adoption of the new techniques, that without treatment 27% of the staff present in both May and September ceased to carry coagulase-positive strains This exceeds the "spontaneous reversion-rate" among transient carriers which has been variously assessed between 1% (Gould 1955) and 15% (Rountree and Barbour 1951) Persistence of nasal carriage has been assessed at *15%–30% for different groups, and our figure of 19% is* similar to that of Hutchison et al (1957) and others *Half* of these nurses persisted in carrying a given strain 48% of the 41 nurses were negative on both occasions, but their progress was not followed in detail during the intervening months

The importance of umbilical carriage has been emphasised by Jellard (1957), who showed that 70% of infants had contaminated cords by the fourth day of life This figure was halved by the regular application of triple dye to the cord Our small series of umbilical swabs (only 3 out of 14 were positive) seems to correspond to Jellard's treated group and we feel that, provided adequate care is given to the umbilicus, it need not become an important source of organisms

It thus seems probable that the epidemic in Hospital A began with the nurse who had crops of boils In the nursery, once infection was introduced, the presence of staphylococci was perpetuated by transfer from cot to cot by hand or aerial transfer, thence to the mother's breast via the milk In Hospital C, however, dust may have played a more important part in cross-infection between women in the same ward

This sequence provides a basis for methods of control, which are thus designed to prevent the introduction of fresh infection by the epidemic strain, and to eradicate the nursery "reservoir" of infection, by prevention of transfer from staff to infant and from infant to infant.

Summary

A further outbreak of staphylococcal infection in two maternity units produced 27 maternal breast abscesses The staphylococcal strain responsible was the phage-type 80/81

The infant was found to be a frequent source of maternal infection and was usually contaminated either directly, or by aerial transmission, from staff carriers The transfer of staphylococci from the infant to the maternal breast milk is important in the pathogenesis of breast abscess

Neonatal sepsis rates were assessed before and after the introduction of control measures Maternal and infant nasal carrier-rates over a three months' period (in the absence of severe sepsis) were investigated The staff carrier-rates were assessed on three occasions in ten months

It is concluded that a nursery may be "seeded" with staphylococci from a nasal carrier among the staff, and that a nursery "reservoir" of staphylococci may persist by hand or air transfer from infant to infant An infant carrying staphylococci may transmit the organism to the mother's breast, either directly via a cracked nipple, or by inoculation of the breast milk, and a breast abscess may then develop

This work was done during the tenure by one of us (J A M) of the Lady King scholarship and was supported by a grant from that fund Our thanks are due to Prof J L Wright, Prof J A R Miles, Dr M McGeorge, Mr H Shott, and to the matrons and staffs of the hospitals, for their advice and cooperation

REFERENCES

Battersby, E F, Stringer, H C W (1954) *N.Z med J* 53, 420
Beaven, D W, Burry, A F (1956) *Lancet*, ii, 211
Blowers, R, Wallace, K R (1955) *ibid* i, 1250
Briggs, J N (1957) *Canad med Ass J* 76, 269
Burkinshaw, J, Hamer, J, Swier, J (1957) Thesis for the Course in Preventive Medicine, University of Otago Medical School, Dunedin
Douglas, A, Knights, H T (1956) *N.Z med J* 55, 378
Duncan, J T, Walker, J (1942) *J Hyg, Lond* 42, 474
Gairdner, D M T (1954) Recent Advances in Pædiatrics London, p 97
Gillespie, W A, Alder, V B (1957) *Lancet*, i, 632.
Gould, J C (1955) *J Hyg, Lond* 53, 379
Hutchison, J G P, Green, C A, Grimson, T A (1957) *J clin. Path* 10, 92
Jellard, J (1957) *Brit med J* i, 925
McDonald, S, Timbury, M C (1957) *Lancet*, ii, 863
Markham, N P, Shott, H C. W (1958) *N Z med J* 58, 55
Rountree, P M, Barbour, R G H (1951) *J Path Bact* 63, 313
— Freeman, B M (1955) *Med J Aust* ii, 157
— Isbister, J S, Dods, L, Cook, C E, Mayes, B T (1956) Staphylococcal Infections in Maternity Hospitals National Health and Medical Research Council Special Report Series No 7 Canberra, Australia
Shaffer, T E, Sylvester, R F, Baldwin, J N, Rheins, M S (1957) *Amer J publ Hlth*, 47, 990
Waller, H (1946) *Arch Dis Childh* 21, 1
Williams, R E O (1956) *Bull Hyg, Lond* 31, 965
Wysham, D N, Mulhern, M E, Navarre, G C., La Veck, G D, Kennan, A L, Giedt, W R (1957) *New Engl J Med* 257, 304

ACUTE LEUKÆMIA IN AN INFANT FOLLOWING EXCESSIVE INTRAUTERINE IRRADIATION

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LEUKÆMIA seldom occurs below the age of one, and is then peculiarly intractable In reporting such a case here, our main purpose is to discuss its ætiology After the infant's death the suspicion arose that its mother might have been given an unusually heavy dose of diagnostic X rays during pregnancy, and that this had something to do with the leukæmia (Stewart et al 1956) Calculations and experiment confirmed that the child must have received a large quantity of X rays during the latter part of intrauterine life They also showed how this quantity could have been much reduced

Case-report

At the age of 10 months the baby was sent to our hospital with a pustular rash For about six weeks she had bruised readily and for two weeks she had been very pale

She was a fourth child, and, though the three siblings were normal, there had been some toxæmia in each pregnancy, all the fœtuses being very large The mother was very obese (238 lb), and in this fourth pregnancy, because of doubt about the position of the fœtus, three X-ray examinations were undertaken, with a total of five exposures of which three were anteroposterior, and two were lateral projections The fœtus initially lay as a breech and then transversely After an external version, surgical induction was performed at an estimated date of 37 weeks Labour was quick and uncomplicated, and the infant was apparently normal, weighing *9 lb 12 oz* She developed much as her siblings had done, and was bright and cheerful, though always a rather capricious feeder She sat up at 7 months, and at 10 months had two teeth

FŒTAL EXPOSURES

Date	View	Kv	mAs	Focal skin distance	Skin dose	Central fœtus depth	Dose to centre of fœtus
Nov. 15	A.P.	78	550	19 in.	53·2r	4·0 in.	6·15r
„ 15	Lat. L. to R.	81	600	20 in.	55·9r	3·5 in.	8·4r
„ 28	A.P.	76	500	19 in.	46·0r	4·0 in.	5·3r
Dec. 7	A.P.	76	500	19 in.	46·0r	4·5 in.	4·1r
„ 7	Lat. L. to R.	76	500	22 in.	34·2r	6·0 in.	1·4r
Total							25·35r

Dose to centre of fœtal skull 57·3r.
Dose to mean centre of fœtal tibiæ 23·6r.
Integral dose to whole fœtal body app. 0·1 mega-gram-röntgen.
A.P. = anteroposterior. Lat. = lateral. L. to R. = left to right.

When she was admitted, the lymph-nodes on both sides of the neck were slightly enlarged, the spleen could be felt 2 in., and the liver 1½ in. below the costal margin. The blood contained only 3·5 g. hæmoglobin per 100 ml., and the white-cell count was 41,000 per c.mm. rising to 70,000 (1400 neutrophil polymorphs, 14,700 lymphocytes, 700 monocytes, 5600 myelocytes, and 47,600 blast cells with very primitive nuclei and huge nucleoli), platelets 36,000 per c.mm. The findings resembled those of the "myelomonocytic (Naegeli)" type of acute granulocytic leukæmia usually seen in much older patients.

The baby was transfused and given prednisone 20 mg. daily, without improvement. She developed a staphylococcal septicæmia and died on the 11th hospital day. Postmortem examination confirmed the diagnosis of acute granulocytic leukæmia and staphylococcal pyæmia.

The Radiation Exposures

The mother had been radiographed for fœtal presentation on Nov. 15, Nov. 28, and Dec. 7 (the day before delivery). Because of her obesity, the exposure factors were much greater than is usual. For the anteroposterior examinations she was supine, and for both laterals she lay on her right side. No added filter was used for any of the exposures.

The table shows the focal distances and the location of the various parts of the fœtus, as estimated from an analysis of the films, making allowance for radiographic magnification and the sag of the fœtal region during the lateral exposures. There must necessarily be some inaccuracy in such estimates, but we believe that these are approximately correct. It is worth noting that had the *first lateral* exposure (Nov. 15) been given with the patient lying on her left side instead of the right it would have contributed only 1·4r instead of 8·4r.

The röntgen exposure doses were measured with a calibrated Victoreen r-meter. An average back scatter factor of 1·26 was found experimentally with a pressed wood phantom and a flat plate ionisation chamber. The chamber was also used to determine the percentage depth dose in pressed wood, and the values obtained were used in calculating the röntgen exposure received at the centre of the fœtus.

In this analysis we have chosen to estimate the radiation exposure to the centre of the fœtal skeleton. There appear to be three main methods of stating the radiation exposure for correlation with leukæmia—namely (*a*) the average dose to the fœtus (Bewley et al. 1957), (*b*) the integral dose to the whole body (Wheatley and Geilinger 1957) and (*c*) the dose to the centre of the fœtal skeleton (Clayton et al. 1957). Any assessment of the average dose to the fœtus is difficult, and so is the application to the fœtal body of the method for estimating the integral dose. The calculation of the dose to the centre of the fœtal skeleton is simpler and more accurate. However, we have attempted a very rough estimate of the integral dose, and we include it to indicate the order of its magnitude. We also add estimates of the dose received by other parts of the fœtal skeleton.

Discussion

In older children leukæmia is almost exclusively lymphocytic, but in the very young it is commonly granulocytic. In the very rare cases of congenital leukæmia, too, there is a great predominance of granulocytic forms—e.g., 28 granulocytic to 4 lymphocytic (Reimann et al. 1955). It appears permissible to group together congenital leukæmias and those occurring up to the age of perhaps one year, since they tend to show similar and distinctive clinical features (especially a hyperacute course) and hæmatological findings. The question arises whether their ætiology may be equally distinctive.

In 1956 Stewart et al. published a preliminary report which showed that in a group of children dying from leukæmia and other malignant diseases diagnostic irradiation of the mother's abdomen during pregnancy had been significantly more frequent than in a control group. These findings suggested that leukæmia in children could sometimes be caused by diagnostic irradiation of the maternal pelvis during pregnancy. In criticism of this conclusion (Rabinowitch 1956, 1957, Reid 1957, Jackson 1958, Parlee 1958) the most important argument has been that the dose of X rays received by the fœtus during such exposures must have been far too small to cause leukæmia. Thus the average dose of 1–2·5r (Rabinowitch) is insignificant when compared with the doses administered to patients with ankylosing spondylitis (Court-Brown and Doll 1957) or to those inhabitants of Hiroshima and Nagasaki who later developed leukæmia. Authors who have been inclined to accept the leukæmogenic action of diagnostic irradiation in pregnancy have concluded that "a dose of 2500mr doubles the leukæmia rate" (Hodges 1958).

Our case shows that, whatever the *average* dose given to pregnant women and their fœtuses, it is possible, using standard techniques and only those exposures which are regarded as essential for the safe conduct of a difficult obstetrical case, to administer very much higher doses than have yet been mentioned in the discussion of Stewart's figures. Indeed, the quantity of radiation received by the fœtus in our case (a mean of about 25r) was about the same as that probably received by the majority of those inhabitants of Hiroshima and Nagasaki who survived the atomic bombing at distances of 1500–2000 metres from the hypocentre (mean 50 rem)—a dose great enough to raise the leukæmia incidence among them by 200–300% compared with people in the "control" zone at more than 2000 metres from the hypocentre (Lewis 1957). Hence, to account for leukæmia in cases resembling ours, it is unnecessary to invoke the possibly very high sensitivity of the fœtal hæmopoietic system to the effects of ionising radiation. Again, accepting with reservations the estimates of the integral body dose, that received by irradiated spondylitics is (allowing for the difference in body-weight) in most cases only six to twenty times as large as that received by our fœtus, and not several hundred times, as deduced by Rabinowitch.

If irradiation caused the leukæmia in our patient, the latent period between irradiation and the onset of the leukæmia was much shorter than that in Japan, which was upwards of 3 years (Moloney and Lange 1954a), or in the British series of irradiated spondylitics (2–5 years, Court-Brown and Doll 1957). But since we were dealing with a very young infant, this short latency does not rule out a causal relationship. It may be significant that the leukæmia was granulocytic, for, except in Simpson et al. (1956) cases of lymphocytic leukæmia following irradiation of the thymus in childhood, nearly all reported post-irradiation leukæmias have been granulocytic—either acute or chronic (Court-Brown and Doll 1957, Moloney and Lange 1954b). It seems advisable to analyse future cases of granulocytic leukæmia in infancy ("congenital" and "acquired") with particular care

Australian National Health and Medical Research Council (Rountree et al 1956) (*which contains an extensive bibliography*), two points from which have been adopted here the use of 2% gentian violet in 70% alcohol for local application to pustules and the discontinuance of routine eye-drops at birth

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It thus seems probable that the epidemic in Hospital A began with the nurse who had crops of boils In the nursery, once infection was introduced, the presence of staphylococci was perpetuated by transfer from cot to cot by hand or aerial transfer, thence to the mother's breast via the milk In Hospital C, however, dust may have played a more important part in cross-infection between women in the same ward

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REFERENCES

Battersby, E F, Stringer, H C W (1954) *N.Z med J* 53, 420
Beaven, D W, Burry, A F (1956) *Lancet*, ii, 211
Blowers, R, Wallace, K R (1955) *ibid* i, 1250
Briggs, J N (1957) *Canad med Ass J* 76, 269
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Douglas, A, Knights, H T (1956) *N.Z med J* 55, 378
Duncan, J T, Walker, J (1942) *J Hyg, Lond* 42, 474
Gairdner, D M T (1954) Recent Advances in Pædiatrics London, p 97
Gillespie, W A, Alder, V B (1957) *Lancet*, i, 632
Gould, J C (1955) *J Hyg, Lond* 53, 379
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— Freeman, B *M* (1955) *Med J Aust* ii, 157
— Isbister, J S, Dods, L, Cook, C E, *Mayes*, B T (1956) Staphylococcal Infections in Maternity Hospitals National Health and Medical Research Council Special Report Series No 7 Canberra, Australia
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FOLLOWING EXCESSIVE INTRAUTERINE IRRADIATION

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Leukæmia seldom occurs below the age of one, and is then peculiarly intractable In reporting such a case here, our main purpose is to discuss its ætiology After the infant's death the suspicion arose that its mother might have been given an unusually heavy dose of diagnostic X rays during pregnancy, and that this had something to do with the leukæmia (Stewart et al 1956) Calculations and experiment confirmed that the child must have received a large quantity of X rays during the latter part of intrauterine life They also showed how this quantity could have been much reduced

Case-report

At the age of 10 months the baby was sent to our hospital with a pustular rash For about six weeks she had bruised readily and for two weeks she had been very pale

She was a fourth child, and, though the three siblings were normal, there had been some toxæmia in each pregnancy, all the fœtuses being very large The mother was very obese (238 lb), and in this fourth pregnancy, because of doubt about the position of the fœtus, three X-ray examinations were undertaken, with a total of five exposures of which three were anteroposterior, and two were lateral projections The fœtus initially lay as a breech and then transversely After an external version, surgical induction was performed at an estimated date of 37 weeks Labour was quick and uncomplicated, and the infant was apparently normal, weighing 9 lb 12 oz She developed much as her siblings had done, and was bright and cheerful, though always a rather capricious feeder She sat up at 7 months, and at 10 months had two teeth

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Date	View	Kv	mAs	Focal skin distance	Skin dose	Central fœtus depth	Dose to centre of fœtus
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Total							25·35r

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Dose to mean centre of fœtal tibiæ 23·6r.
Integral dose to whole fœtal body app. 0·1 mega-gram-röntgen.
A.P = anteroposterior. Lat. = lateral. L. to R. = left to right.

When she was admitted, the lymph-nodes on both sides of the neck were slightly enlarged, the spleen could be felt 2 in., and the liver 1½ in. below the costal margin. The blood contained only 3·5 g. hæmoglobin per 100 ml., and the white-cell count was 41,000 per c.mm. rising to 70,000 (1400 neutrophil polymorphs, 14,700 lymphocytes, 700 monocytes, 5600 myelocytes, and 47,600 blast cells with very primitive nuclei and huge nucleoli), platelets 36,000 per c.mm. The findings resembled those of the "myelomonocytic (Naegeli)" type of acute granulocytic leukæmia usually seen in much older patients.

The baby was transfused and given prednisone 20 mg. daily, without improvement. She developed a staphylococcal septicæmia and died on the 11th hospital day. Postmortem examination confirmed the diagnosis of acute granulocytic leukæmia and staphylococcal pyæmia.

The Radiation Exposures

The mother had been radiographed for fœtal presentation on Nov. 15, Nov. 28, and Dec. 7 (the day before delivery). Because of her obesity, the exposure factors were much greater than is usual. For the anteroposterior examinations she was supine, and for both laterals she lay on her right side. No added filter was used for any of the exposures.

The table shows the focal distances and the location of the various parts of the fœtus, as estimated from an analysis of the films, making allowance for radiographic magnification and the sag of the fœtal region during the lateral exposures. There must necessarily be some inaccuracy in such estimates, but we believe that these are approximately correct. It is worth noting that had the first lateral exposure (Nov. 15) been given with the patient lying on her left side instead of the right it would have contributed only 1·4r instead of 8·4r.

The röntgen exposure doses were measured with a calibrated Victoreen r-meter. An average back scatter factor of 1·26 was found experimentally with a pressed wood phantom and a flat plate ionisation chamber. The chamber was also used to determine the percentage depth dose in pressed wood, and the values obtained were used in calculating the röntgen exposure received at the centre of the fœtus.

In this analysis we have chosen to estimate the radiation exposure to the centre of the fœtal skeleton. There appear to be three main methods of stating the radiation exposure for correlation with leukæmia—namely (*a*) the average dose to the fœtus (Bewley et al. 1957), (*b*) the integral dose to the whole body (Wheatley and Geilinger 1957) and (*c*) the dose to the centre of the fœtal skeleton (Clayton et al. 1957). Any assessment of the average dose to the fœtus is difficult, and so is the application to the fœtal body of the method for estimating the integral dose. The calculation of the dose to the centre of the fœtal skeleton is simpler and more accurate. However, we have attempted a very rough estimate of the integral dose, and we include it to indicate the order of its magnitude. We also add estimates of the dose received by other parts of the fœtal skeleton.

Discussion

In older children leukæmia is almost exclusively lymphocytic, but in the very young it is commonly granulocytic. In the very rare cases of congenital leukæmia, too, there is a great predominance of granulocytic forms—e.g., 28 granulocytic to 4 lymphocytic (Reimann et al. 1955). It appears permissible to group together congenital leukæmias and those occurring up to the age of perhaps one year, since they tend to show similar and distinctive clinical features (especially a hyperacute course) and hæmatological findings. The question arises whether their ætiology may be equally distinctive.

In 1956 Stewart et al. published a preliminary report which showed that in a group of children dying from leukæmia and other malignant diseases diagnostic irradiation of the mother's abdomen during pregnancy had been significantly more frequent than in a control group. These findings suggested that leukæmia in children could sometimes be caused by diagnostic irradiation of the maternal pelvis during pregnancy. In criticism of this conclusion (Rabinowitch 1956, 1957, Reid 1957, Jackson 1958, Parlee 1958) the most important argument has been that the dose of X rays received by the fœtus during such exposures must have been far too small to cause leukæmia. Thus the average dose of 1–2·5r (Rabinowitch) is insignificant when compared with the doses administered to patients with ankylosing spondylitis (Court-Brown and Doll 1957) or to those inhabitants of Hiroshima and Nagasaki who later developed leukæmia. Authors who have been inclined to accept the leukæmogenic action of diagnostic irradiation in pregnancy have concluded that "a dose of 2500mr doubles the leukæmia rate" (Hodges 1958).

Our case shows that, whatever the *average* dose given to pregnant women and their fœtuses, it is possible, using standard techniques and only those exposures which are regarded as essential for the safe conduct of a difficult obstetrical case, to administer very much higher doses than have yet been mentioned in the discussion of Stewart's figures. Indeed, the quantity of radiation received by the fœtus in our case (a mean of about 25r) was about the same as that probably received by the majority of those inhabitants of Hiroshima and Nagasaki who survived the atomic bombing at distances of 1500–2000 metres from the hypocentre (mean 50 rem)—a dose great enough to raise the leukæmia incidence among them by 200–300% compared with people in the "control" zone at more than 2000 metres from the hypocentre (Lewis 1957). Hence, to account for leukæmia in cases resembling ours, it is unnecessary to invoke the possibly very high sensitivity of the fœtal hæmopoietic system to the effects of ionising radiation. Again, accepting with reservations the estimates of the integral body dose, that received by irradiated spondylitics is (allowing for the difference in body-weight) in most cases only six to twenty times as large as that received by our fœtus, and not several hundred times, as deduced by Rabinowitch.

If irradiation caused the leukæmia in our patient, the latent period between irradiation and the onset of the leukæmia was much shorter than that in Japan, which was upwards of 3 years (Moloney and Lange 1954a), or in the British series of irradiated spondylitics (2–5 years, Court-Brown and Doll 1957). But since we were dealing with a very young infant, this short latency does not rule out a causal relationship. It may be significant that the leukæmia was granulocytic, for, except in Simpson et al. (1956) cases of lymphocytic leukæmia following irradiation of the thymus in childhood, nearly all reported post-irradiation leukæmias have been granulocytic—either acute or chronic (Court-Brown and Doll 1957, Moloney and Lange 1954b). It seems advisable to analyse future cases of granulocytic leukæmia in infancy ("congenital" and "acquired") with particular care

Australian National Health and Medical Research Council (Rountree et al 1956) (which contains an extensive bibliography), two points from which have been adopted here the use of 2% gentian violet in 70% alcohol for local application to pustules and the discontinuance of routine eye-drops at birth

It seems that there must be a minimum level of sepsis of the third type, since it is not practicable, nor are we convinced of the advisability of treating all nasal carriers of coagulase-positive staphylococci, as it has been suggested (Rountree and Barbour 1951) that carriage of one strain (possibly penicillin-sensitive) may protect against the acquisition of a more virulent or more resistant strain, and it became apparent, with the decrease in amount of sepsis in Hospital B after the adoption of the new techniques, that without treatment 27% of the staff present in both May and September ceased to carry coagulase-positive strains This exceeds the "spontaneous reversion-rate" among transient carriers which has been variously assessed between 1% (Gould 1955) and 15% (Rountree and Barbour 1951) Persistence of nasal carriage has been assessed at 15%–30% for different groups, and our figure of 19% is similar to that of Hutchison et al (1957) and others Half of these nurses persisted in carrying a given strain 48% of the 41 nurses were negative on both occasions, but their progress was not followed in detail during the intervening months

The importance of umbilical carriage has been emphasised by Jellard (1957), who showed that 70% of infants had contaminated cords by the fourth day of life This figure was halved by the regular application of triple dye to the cord Our small series of umbilical swabs (only 3 out of 14 were positive) seems to correspond to Jellard's treated group and we feel that, provided adequate care is given to the umbilicus, it need not become an important source of organisms

It thus seems probable that the epidemic in Hospital A began with the nurse who had crops of boils In the nursery, once infection was introduced, the presence of staphylococci was perpetuated by transfer from cot to cot by hand or aerial transfer, thence to the mother's breast via the milk In Hospital C, however, dust may have played a more important part in cross-infection between women in the same ward

This sequence provides a basis for methods of control, which are thus designed to prevent the introduction of fresh infection by the epidemic strain, and to eradicate the nursery "reservoir" of infection, by prevention of transfer from staff to infant and from infant to infant

Summary

A further outbreak of staphylococcal infection in two *maternity units produced 27 maternal breast abscesses* The staphylococcal strain responsible was the phage-type 80/81

The infant was found to be a frequent source of maternal infection and was usually contaminated either directly, or by aerial transmission, from staff carriers The transfer of staphylococci from the infant to the maternal breast milk is important in the pathogenesis of breast abscess

Neonatal sepsis rates were assessed *before and after* the introduction of control measures Maternal and infant nasal carrier-rates over a three months' period (in the absence of severe sepsis) were investigated The staff carrier-rates were assessed on three occasions in ten months

It is concluded that a nursery may be "seeded" with staphylococci from a nasal carrier among the staff, and *that a nursery "reservoir" of staphylococci may persist* by hand or air transfer from infant to infant An infant carrying staphylococci may transmit the organism to the mother's breast, either directly via a cracked nipple, or by inoculation of the breast milk, and a breast abscess may then develop

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REFERENCES

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Gairdner, D M T (1954) Recent Advances in Pædiatrics London, p 9
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LEUKÆMIA seldom occurs below the age of one, and is then peculiarly intractable In reporting such a case here, our main purpose is to discuss its ætiology After the infant's death the suspicion arose that its mother might have been given an unusually heavy dose of diagnostic X rays during pregnancy, and that this had something to do with the leukæmia (Stewart et al *1956)* Calculations and experiment confirmed that the child must have received a large quantity of X rays during the latter part of intrauterine life They also showed how this quantity *could have been much reduced*

Case-report

At the age of 10 months the baby was sent to our hospital with a pustular rash For about six weeks she had bruised readily and for two weeks she had been very pale

She was a fourth child, and, though the three siblings were normal, there had been some toxæmia in each pregnancy, all the fœtuses being very large The mother was very obese (238 lb), and in this fourth pregnancy, because of doubt about the position of the fœtus, three X-ray examinations were undertaken, with a total of five exposures of which three were anteroposterior, and two were lateral projections The fœtus initially lay as a breech and then transversely After an external version, surgical induction was performed at an estimated date of 37 weeks Labour was quick and uncomplicated, and the infant was apparently normal, weighing 9 lb 12 oz She developed much as her siblings had done, and was bright and cheerful, though always a rather capricious feeder She sat up at 7 months, and at 10 months had two teeth

Fig 2—Lateral and anteroposterior radiographs of skull Twin cannulas introduced.

root diameter of the screw (0 106 in), and the loaded screw, attached to the screwdriver, is passed along the cannula The encased yttrium-90 passes through the drillhole and penetrates the pituitary gland, while the thread of the screw firmly grips the bone Advancement of the source into a central position is easily accomplished by a few turns of the screw which fix it firmly in the required position (fig 3) If the central threaded rod is first unscrewed the screwdriver can be removed without danger of withdrawing the yttrium-loaded screw from the bone (fig 4)

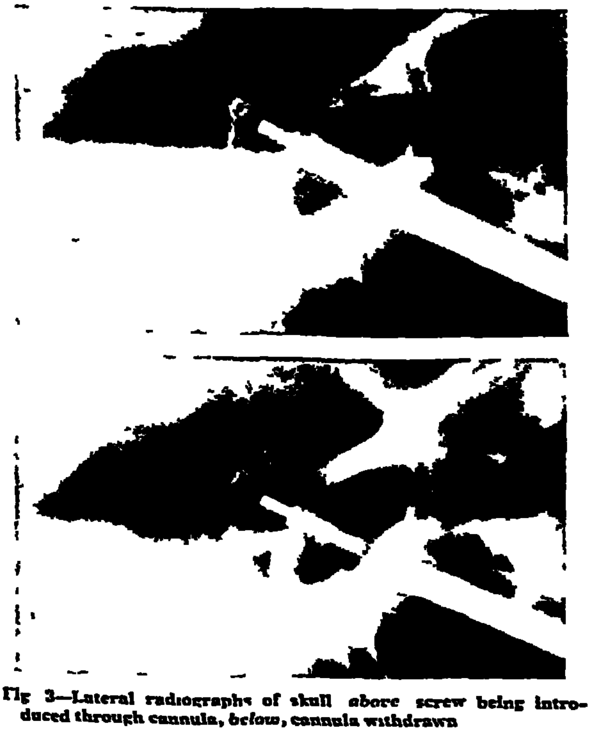

Fig 3—Lateral radiographs of skull *above* screw being introduced through cannula, *below*, cannula withdrawn

Fourteen patients with metastatic mammary cancer, considered unfit for adrenalectomy, have been treated by introducing twin screws each loaded with 5–7 mC yttrium-90 into the pituitary by this method These patients all had advanced disease, and three died from progression of cancer within 8 days of pituitary screw-implantation In all three the gland was entirely destroyed except for a single layer of subcapsular cells That these would probably have failed to survive had the patients lived longer is suggested by the finding of complete destruction of the pituitary in a further patient who died 6 weeks after implantation As in other forms of pituitary ablation, cortisone therapy is required to maintain life after screw-implantation with yttrium-90

We believe that this revised method of radioactive implantation of the pituitary offers distinct advantages over our previous techniques [1 3 4] and ensures that the sources of yttrium-90 are placed with consistent accuracy

We are grateful to Prof C F W Illingworth for allowing us to treat these patients in his unit, and to Mr Angus Macdonald, of the Western Infirmary workshop, and Mr Edward Fahey, of the Regional Physics Department, for technical assistance in constructing the screws and apparatus The postmortem histological examination of the pituitaries was carried out by Dr A T Sandison, of the University Department of Pathology, Western Infirmary

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[3] Forrest, A P M , Peebles Brown D A *Lancet*, 1955 i 1054

[4] Forrest A P M , Peebles Brown, D A , Morris, S R , Illingworth, C F W *ibid* 1956 i, 399

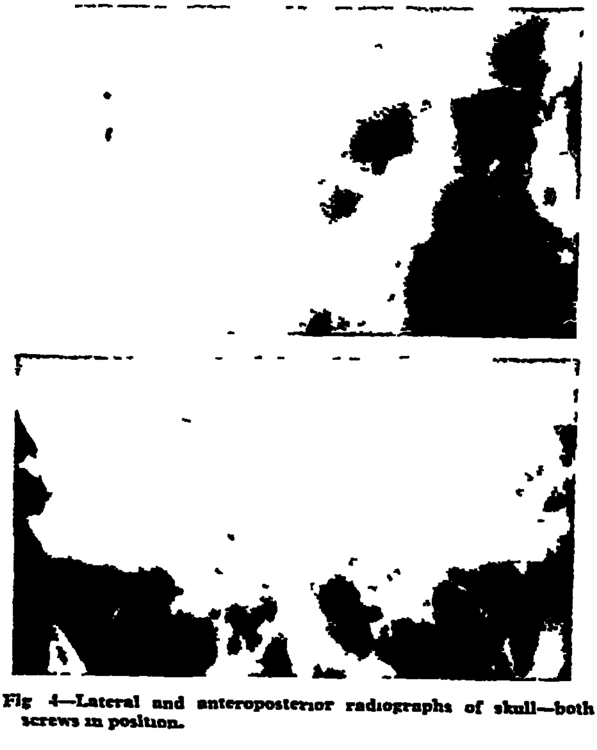

Fig 4—Lateral and anteroposterior radiographs of skull—both screws in position.

as regards exposure to radiation, and to ascertain whether their history of exposure differs from that of the predominantly lymphocytic group of leukæmias in later childhood Possibly the higher leukæmia incidence found by Stewart et al may be accounted for chiefly by "exceptional" cases like ours

Our patient received during fœtal life a dose of radiation such as has materially increased the leukæmia-rate in an adult population Soon after this infant's mother was examined radiologically, and well before her infant's admission, the technique for obstetrical exposure at our hospital was altered to reduce the amount of radiation received both by mother and fœtus This has been achieved, without any appreciable alteration in the quality of films, by the following means

(1) Additional tube filtration of 2 mm of aluminium
(2) The use of high-speed screens
(3) Doubling the development time of the film
(4) Increasing the anode film distance in erect lateral films of the pelvis from 40 in to 60 in
(5) The use of high kilovoltage techniques

These modifications have resulted in a striking reduction in the X-ray dosage necessary to produce diagnostic films For example if the examinations on our patient, a 17-stone woman, were performed at the present time, the dose to the centre of the fœtus would be approximately 1 9r, or only 8% of that actually received It would be much lower still in the average obstetric case which has been so widely discussed of late

Summary

A 10-month old infant died from acute granulocytic leukæmia

The mother had had three X-ray examinations (five exposures) during late pregnancy Since she was an exceptionally heavy woman, the dose given to her and received by the fœtus was exceptionally large and lay within the range known to be potentially leukæmogenic in adults

Modifications in the technique of radiography which have since been introduced would have diminished the dose received by the fœtus by 92%

The patient reported upon was under the care of Dr J F Landreth, whose permission to publish her record is gratefully acknowledged

REFERENCES

Bewley, D K, Laws, J W, Myddleton, C J (1957) *Brit J Radiol* 30, 286
Clayton, C G, Farmer, F T, Warrick, C K (1957) *ibid* p 291
Court-Brown, W M, Doll R (1957) Leukæmia and Aplastic Anæmia in Patients Irradiated for Ankylosing Spondylitis *Spec Rep med Res Coun, Lond* no 295
Hodges, P C (1958) *J Amer med Ass* 166, 577
Jackson, H (1958) *Lancet*, i, 695
Lewis, E B (1957) *Science*, 125, 965
Moloney, W C, Lange, R D (1954a) *Texas Rep Biol & Med* 12, 887
— — (1954b) *Blood*, 9, 663
Parlee, S S (1958) *Amer J Obstet Gynec* 75, 327
Rabinowitch, J (1956) *Lancet*, ii, 1261
— (1957) *ibid* i, 219
Reid, F (1957) *ibid* p 428
Reimann, D L, Clemmens, R L, Pillsbury, W A (1955) *J Pediat* 46, 415
Simpson, C L, Hempelmann, L H, Fuller, L M (1955) *Radiology*, 64, 840
Stewart, A, Webb, J, Giles, D, Hewitt, D (1956) *Lancet*, ii, 447
Wheatley, B M, Gellinger, J (1957) *in* Court-Brown and Doll, 1957

Preliminary Communication

SCREW-IMPLANTATION OF THE PITUITARY WITH YTTRIUM-90

COMPLETE necrosis of the pituitary gland can be achieved by implanting two 6 mC rods of yttrium-90 into the sella turcica through twin cannulas inserted transnasally (one through either nostril) under radiological control, and this method of treatment may benefit patients with advanced mammary cancer [1] Consistent and trouble-free destruction of the gland depends primarily on placing the two sources of radiation so that one lies in the centre of each half of the gland A disadvantage of our previous method of implantation was that the rods were sometimes deflected into the space between the gland and the wall of the sella turcica, with the result that irradiation of the gland was incomplete In addition, troublesome rhinorrhœa occurred in ten of the fifty-four patients treated This was believed to be due to radiation necrosis of the diaphragma sellæ caused by faulty placing of the rods

A modified technique has therefore been developed, for use with an image amplifier, to fix the rods in the optimum position In this new method the holes in the anterior wall of the sella, through which the rods have been inserted, are plugged, providing an added protection against leakage of cerebrospinal fluid

A cylindrical rod of yttrium oxide (5 × 2 mm, 68 mg)* is encased in a very thin sharp-pointed nylon sheath in which it is held by a small nylon plug After activation in the Harwell pile, BEPO, this unit is fitted into one end of a stainless steel self-tapping orthopædic screw (Sherman screw size 6, $^5/_{32}$" in diameter)† 0 5 in long This end has been drilled to accommodate the nylon-encased rod and the other end has been turned down and screwed with a 6 BA die (fig 1) This portion of the screw accommodates a similarly threaded but loosely fitting screwdriver When the threaded central rod of the screwdriver is tightened, the screw is firmly clamped, and it can be released only when the rod is loosened

By the use of a director apparatus similar to that previously described,[2] twin 4 mm cannulas are introduced, one through each nostril, until their ends lie against the outer wall of the pituitary fossa opposite the middle of the gland (fig 2) Correct alignment of the cannulas is achieved by screening with the image amplifier A diamond-steel drill is introduced down each cannula to cut a hole in the wall of the fossa equivalent to the

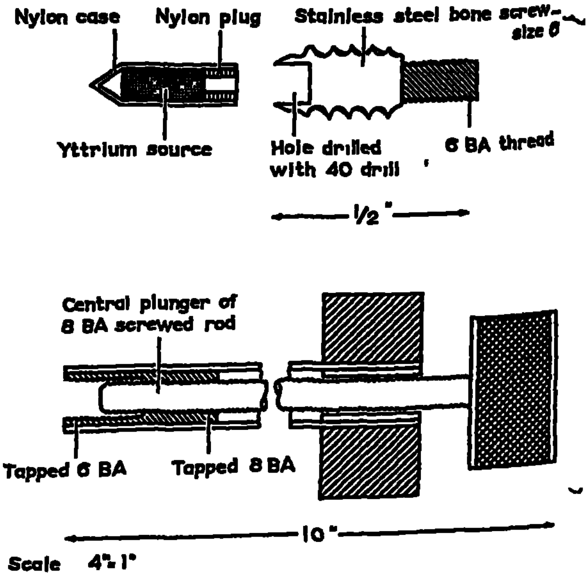
Nylon case
Nylon plug
Stainless steel bone screw-size 6
Yttrium source
Hole drilled with 40 drill
6 BA thread
½"
Central plunger of 8 BA screwed rod
Tapped 6 BA
Tapped 8 BA
10"
Scale 4"=1"

Fig 1—Plan drawing of screw and screwdriver used for yttrium 90 implantation

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* Manufactured by Johnson, Matthey & Co, Ltd
† Supplied by London Splint Company Ltd
[1] Forrest, A P M, Blair, D W, Morris S R, Peebles Brown, D A, Sandison, A T, Valentine, J M, Illingworth, C F W Endocrine Aspects of Breast Cancer, p 46, Edinburgh, 1958
[2] Forrest, A P M *Postgrad med J* 1957, 33, 372

THE LANCET
LONDON 26 JULY 1958

A Memorable Experiment

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The first, and obvious, conclusion that accrued from **Goldblatt**'s work was that the hypertension that arises in the course of structural disease of the kidney may be attributed to impedance of the circulation The next followed quickly on the discovery that in some species, notably the rat,[2] permanent hypertension could be caused by constriction of only one renal artery Such hypertension was found to be followed by the appearance in the opposite kidney of acute arterial necrosis and other lesions characteristic of malignant hypertension which had previously been regarded as inflammatory, and this strengthened the concept of malignant hypertension and simplified the classification of Bright's disease [3] The suggestion that these lesions in the rat are due to spontaneous periarteritis nodosa [4] or pyelonephritis [5] overlooks the fact that they are invariably absent from the " clamped " kidney Likewise the view that hypertension causes arterial necrosis only in the presence of renal excretory failure [5] is not consistent with clinical or experimental facts [6] The work already mentioned also strengthened the clinical suspicion that unilateral renal disease might underlie some cases of hypertension in man, and it is now generally recognised that severe hypertension may occasionally arise in this way and may be dramatically cured, even in the malignant phase, by nephrectomy provided that the primary renal disease is strictly unilateral and that the condition is recognised before significant secondary hypertensive damage has developed in the opposite kidney The detection of this unilateral renal disease is often extremely difficult, for it may take many different forms, from postoperative stenosis of a ureter [7] to pyelonephritis set up by habitual failure to empty the bladder more than once a day [8]

Another early outcome of **Goldblatt**'s experiment was the rediscovery in the normal kidney of the pressor substance renin,[9 10] which had lain buried in the literature for forty years Renin was soon found to be an enzyme [9] producing the polypeptide hypertensin Subsequent developments in chemical technique have made possible first the identification of the inert decapeptide,[11] then the elucidation of the structure of the active octapeptide,[12] and finally the synthesis of this highly active substance which contains as much as 50,000 pressor units per milligramme of nitrogen [13 14] Whether overproduction of renin is responsible for Goldblatt hypertension is still not conclusively proven, but the evidence is very suggestive The strongest evidence relates to the fact that renin is a protein and can be used to prepare a highly specific antibody In animals with renal hypertension passive or active immunity conferred by this antirenin is accompanied by pronounced lowering of the blood-pressure [15] Renin and more recently hypertensin [16] have also been demonstrated in the blood after constriction of the renal artery Hypertension has been maintained for as long as seventeen days in rabbits by continuous intravenous injection of renin,[17] and when such an infusion is discontinued the hypertension persists for about as long as it does when a clip is removed from a renal artery [18]—that is, about four hours A further point relates to the effect of pregnancy During pregnancy in the normal animal the reactivity to renin is lowered,[19] and in rats with Goldblatt hypertension the blood-pressure falls progressively [19 20] It has recently been shown that these two changes are closely related in time [21] The reactivity to hypertensin is not altered in pregnancy [22] The renin hypothesis will not, of course, account for the hypertension which follows total nephrectomy Nor is it clear why the presence of normal kidney tissue tends to mitigate renal hypertension On the other hand, no simple explanation of renoprival hypertension will explain why constricting one renal artery causes hypertension while excising one kidney

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1 *Circulation*, 1958, 17, pp 640–840
2 Wilson, C., Byrom, F B *Lancet*, 1939, i, 136
3 Ellis A W M *ibid* 1942, i, 1
4 Goldblatt, H F *Circulation* 1958, 17, 645
5 Goldblatt, H F *Physiol Rev* 1947, 27, 120
6 *Lancet*, 1958, i, 1109
7 Marshall, F C , Zervas, N , Olszewski, J *Canad med Ass J* 1957, 76, 576
8 Nesbit, R M *Circulation*, 1958, 17, 695
9 Braun-Menendez, E , Fasciolo, J C , Leloir, L F , Munoz, J M *J Physiol* 1940, 98, 283
10 Page I H , Helmer, O M *J exp Med* 1940, 71, 29
11 Elliott, D F , Peart, W S *Nature, Lond* 1956, 177, 527
12 Skeggs, L T , Lentz, K E , Kahn, J R , Shumway, N P , Woods, K J *J exp Med* 1956 104, 193
13 Rittel, W , Iselin, B Kappeler, H , Riniker, B , Schwyzer, R *Helv chim Acta* 1957, 40, 614
14 Bumpus, F M , Schwarz, H , Page, I H *Circulation*, 1958, 17, 664
15 Wakerlin, G C *ibid* p 653
16 Skeggs, L T , Kahn, J R *ibid* p 659
17 Blacket, R B , Depoorter A , Pickering, G W , Sellers, A M , Wilson, G M *Clin Sci* 1950, 9, 223
18 Byrom, F B Dodson, L F *ibid* 1949, 8, 1
19 Harrison, T R , Grollman, A , Williams, J R *Amer J Physiol* 1940, 128, 716
20 Wilson C , Byrom, F B *Quart J Med* 1941, 10, 65
21 Mackaness, G B , Dodson, L F *Brit J exp Path* 1957, 38, 628
22 Dodson, L F *ibid* p 635

Reviews of Books

The First Ten Years of the World Health Organization

Geneva W H O 1958 Pp 538 To be had from H M Stationery Office 20s (paper backed), 25s (cloth)

IT was natural and proper that the World Health Organisation should celebrate the first ten years of its existence with a commemorative volume Apart from its own official reports and proceedings, no account of its work as a whole has been written since Goodman's more general and historical book on *International Health* was published in 1952

Beginning with a brief summary of the evolution of international health since the first international Sanitary Conference in 1851, in which tribute is paid to its predecessor organisations, rather more space is given to the establishment of W H O The bulk of the book is a plain factual description of its work under some twenty "functional" headings There are 13 useful appendices giving tabular information on such matters as expert panels, staff, and finance, and many good illustrations and maps It suffers from the defect of most official publications (except the Authorised Version of the Bible) in that neither by phrase, style, or presentation does it do much to help the reader to see the drama of achievement behind the official prose This is perhaps unavoidable, but the absence of a bibliography and adequate references is less excusable A spot check of the index also revealed some gaps Nevertheless, this is an important publication and gives an accurate and adequate account of an expanding and successful ten years Though hardly comparable to the conterminous first ten years of the National Health Service, they have been impressive, particularly when one remembers that for every £ that the whole world spends on W H O, we spend on the N H S over £70

The Strategy of Chemotherapy

8th Symposium of the Society for General Microbiology Editors S T COWAN and E ROWATT London Cambridge University Press 1958 Pp 360 35s

THE chemotherapeutic agents and antibiotics in clinical use have not been designed in any rational scientific way The failure of the logical approach to the chemotherapy of infections is largely due to lack of detailed information about the metabolism of both the invader and the host In this symposium, organised by Dr E F Gale, the 16 contributions review present-day knowledge of this subject and speculate on the lines along which future research might be usefully directed

Prof Robert Knox believes that it would be helpful to consider the strategy of chemotherapy at three different levels the fundamental level, the level of the interactions between microorganisms and the individual host, and the epidemiological level This useful concept is well developed in an article that integrates these different approaches As he points out "it is often difficult for workers in one branch to understand the thoughts or even the language of workers in other branches"

The rest of the book is concerned with fundamental problems It is a pity that there is only the briefest reference to the contribution made by bacterial genetics to our understanding of the mechanisms of drug resistance Separate and detailed consideration is given to bacterial-cell-wall structure and the way chemotherapeutic agents may interfere with its integrity, to similarities and differences in energy-supplying reactions and protein synthesis in microorganisms and host cells, to the action of metal-binding agents, to the design of antimetabolites, to the selective inhibition of virus multiplication and lethal synthesis, and to chemotherapeutic synergy in its widest sense The topics covered from the biochemical viewpoint are therefore numerous and varied, throughout, the importance of and the reasons for selective toxicity are stressed

Full of well-documented information and useful references, the book will provide research-workers with plenty of ideas Its title, however, is perhaps rather misleading It does not deal with strategy at the clinical level, and readers who turn to it with that in mind may find evaluation of biochemical problems rather hard going

Basic Cardiology

T E GUMPERT, M B, F R C P, physician, Royal Hospital, Sheffield, and Jessop Hospital for Women, Sheffield Bristol John Wright 1958 Pp 176 25s

Dr Gumpert has arranged his valuable lectures on cardiology in a small monograph to bridge the gap between the specialised textbooks and the concentrated account found in more general books It is full of common sense and very readable Indeed, some readers may wonder whether common sense has not in places gone too far, at the cost of neglecting physiological and pathological principles, particularly in the chapter on congenital heart-disease Cyanosis in pulmonary stenosis is attributed partly to the degree of pulmonary obstruction interfering with oxygenation, and the left-to-right shunt in atrial septal defect is thought to be due to gravity

In a controversial chapter on systolic murmurs most innocent systolic murmurs are attributed to functional mitral regurgitation It ends with a question "When is a murmur not a murmur? A murmur is not a murmur when it is the only abnormality which can be found in the course of a full cardiological investigation in a patient who is entirely without symptoms" This may be dangerous teaching, for such a murmur might be a clue to a high output state, or to slight valve disease, unimportant in itself, but a possible root for bacterial endocarditis

Psychobiology

A Science of Man ADOLF MEYER M D, late Henry Phipps professor of psychiatry, Johns Hopkins University Compiled and edited by EUNICE E WINTERS and ANNA MAE BOWERS Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 257 50s

THE first Salmon memorial lecture was delivered by Adolf Meyer in April, 1932 He subsequently revised the lectures for publication but had not completed the task when he died Miss Winters and Miss Bowers, who helped him in the preparation of this and other writings, undertook the heavy work of selecting, from the abundant material which he left, an adequate and telling exposition of his basic ideas "Respect for the Meyerian language and style" was uppermost in their minds, and Meyer wrote a peculiarly involved English, full of abstract nouns, which did no justice to the vigour of his thought and to the wide experience on which his generalisations were founded His old pupils will read these lectures with keen appreciation and a grateful recollection of what they owe to this great teacher, but it is doubtful whether many other readers will penetrate the thicket of words to find the wisdom hidden in them The editors fortunately provide an appendix in which many of the terms used by Meyer are defined and their meaning is amplified

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The Heinemann Series on Sex Education (I Parents' Privilege II. A Story About You III What's Happening to Me? IV Learning About Love V Sex Facts and Attitudes London Heinemann Medical Books 1958 Each vol 7s 6d) —These small books, each of 60–80 pages, do not really form a series, in the sense that one leads to the next, but are intended to give information and advice on sexual anatomy and physiology, and the problems of behaviour and conduct arising from sex, to parents of children and to young people of different ages There is much overlapping The information given by the authors, Marion O Lerrigo and Helen Southard, is accurate and the advice sane and not over-emphatic The familiar diagrams probably convey their meaning, other illustrations fall below the standard of the letterpress The transatlantic origin of the books is apparent but not obtrusive (dating, petting, and necking have no inverted commas) How far early familiarity with pelvic anatomy and physiology will make for happier love-making, marriage, and parenthood is anyone's guess, but if they are wanted here are the facts

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16 Skeggs, L T, Kahn, J R *ibid* p 659
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18 Byrom, F B, Dodson L F *ibid* 1949, 8 1
19 Harrison, T R, Grollman A, Williams J R *Amer J Physiol* 1940, 128 716.
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[12] Skeggs L T Lentz K E Kahn, J R, Shumway N P, Woods, K J *J exp Med* 1956 104 193
[13] Rittel W Iselin, B Kappeler H, Riniker, B, Schwyzer, R *Helv chim Acta* 1957 40, 614
[14] Bumpus, F M, Schwarz, H, Page, I H *Circulation*, 1958, 17, 664
[15] Wakerlin G C *ibid* p 653
[16] Skeggs, L T, Kahn J R *ibid* p 659
[17] Blacket R B Depoorter, A Pickering, G W, Sellers A M, Wilson, G M *Clin Sci* 1950 9 223
[18] Byrom, F B, Dodson L F *ibid* 1949, 8, 1
[19] Harrison T R, Grollman A, Williams J R *Amer J Physiol* 1940, 128 716
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When RICHARD BRIGHT in 1836 called attention to the association between enlargement of the heart and chronic disease of the kidney, he was in effect asking the first of a series of questions which have taxed the resources of subsequent generations of students For over a hundred years progress, depending as it did on observation, inference, and intuition, was inevitably slow, but it nevertheless became clear that, while high blood-pressure could derive from demonstrable kidney disease, it could also occur in its absence The later recognition that this *essential* hypertension could cause renal damage did nothing to simplify the task of those who were patiently trying to bring order out of chaos The year 1933 witnessed an abrupt increase in both the breadth and the tempo of research, for it was in that year that H F GOLDBLATT, in a historic experiment, showed that in animals simply constricting both renal arteries or one renal artery after excision of the opposite kidney produced a form of sustained hypertension which tallied in most essential respects with the disease in man To mark the 25th anniversary of this experiment the University of Michigan organised a conference on Basic Mechanisms of Arterial Hypertension, at which Dr GOLDBLATT was guest of honour The proceedings of this conference have now been published in a special issue of *Circulation*[1]

The first, and obvious, conclusion that accrued from GOLDBLATT's work was that the hypertension that arises in the course of structural disease of the kidney may be attributed to impedance of the circulation The next followed quickly on the discovery that in some species, notably the rat,[2] permanent hypertension could be caused by constriction of only one renal artery Such hypertension was found to be followed by the appearance in the opposite kidney of acute arterial necrosis and other lesions characteristic of malignant hypertension which had previously been regarded as inflammatory, and this strengthened the concept of malignant hypertension and simplified the classification of Bright's disease[3] The suggestion that these lesions in the rat are due to spontaneous periarteritis nodosa[4] or pyelonephritis[5] overlooks the fact that they are invariably absent from the " clamped " kidney Likewise the view that hypertension causes arterial necrosis only in the presence of renal excretory failure[5] is not consistent with clinical or experimental facts[6] The work already mentioned also strengthened the clinical suspicion that unilateral renal disease might underlie some cases of hypertension in man, and it is now generally recognised that severe hypertension may occasionally arise in this way and may be dramatically cured, even in the malignant phase, by nephrectomy provided that the primary renal disease is strictly unilateral and that the condition is recognised before significant secondary hypertensive damage has developed in the opposite kidney The detection of this unilateral renal disease is often extremely difficult, for it may take many different forms, from postoperative stenosis of a ureter[7] to pyelonephritis set up by habitual failure to empty the bladder more than once a day[8]

Another early outcome of GOLDBLATT's experiment was the rediscovery in the normal kidney of the pressor substance renin,[9] [10] which had lain buried in the literature for forty years Renin was soon found to be an enzyme[9] producing the polypeptide hypertensin Subsequent developments in chemical technique have made possible first the identification of the inert decapeptide,[11] then the elucidation of the structure of the active octapeptide,[12] and finally the synthesis of this highly active substance which contains as much as 50,000 pressor units per milligramme of nitrogen[13] [14] Whether overproduction of renin is responsible for Goldblatt hypertension is still not conclusively proven, but the evidence is very suggestive The strongest evidence relates to the fact that renin is a protein and can be used to prepare a highly specific antibody In animals with renal hypertension passive or active immunity conferred by this antirenin is accompanied by pronounced lowering of the blood-pressure[15] Renin and more recently hypertensin[16] have also been demonstrated in the blood after constriction of the renal artery Hypertension has been maintained for as long as seventeen days in rabbits by continuous intravenous injection of renin,[17] and when such an infusion is discontinued the hypertension persists for about as long as it does when a clip is removed from a renal artery[18]—that is, about four hours A further point relates to the effect of pregnancy During pregnancy in the normal animal the reactivity to renin is lowered,[19] and in rats with Goldblatt hypertension the blood-pressure falls progressively[19] [20] It has recently been shown that these two changes are closely related in time[21] The reactivity to hypertensin is not altered in pregnancy[22] The renin hypothesis will not, of course, account for the hypertension which follows total nephrectomy Nor is it clear why the presence of normal kidney tissue tends to mitigate renal hypertension On the other hand, no simple explanation of renoprival hypertension will explain why constricting one renal artery causes hypertension while excising one kidney does not On the whole the prevailing opinion is that renal and renoprival hypertension are not directly related to one another

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[1] *Circulation*, 1958, 17 pp 640–840
[2] Wilson C, Byrom F B *Lancet*, 1939, i, 136
[3] Ellis A W M *ibid* 1942, i, 1
[4] Goldblatt, H F *Circulation* 1958 17 645
[5] Goldblatt H F *Physiol Rev* 1947, 27, 120
[6] *Lancet*, 1958, i, 1109
[7] Marshall, F C, Zervas, N, Olszewski, J *Canad med Ass J* 1957, 76, 576
[8] Nesbit, R M *Circulation*, 1958, 17, 695
[9] Braun-Menendez, E, Fasciolo, J C, Leloir, L F, Munoz, J M *J Physiol* 1940 98, 283
[10] Page, I H, Helmer, O M *J exp Med* 1940, 71 29
[11] Elliott, D F, Peart, W S *Nature Lond* 1956, 177, 527
[12] Skeggs L T, Lentz, K E Kahn, J R, Shumway, N P, Woods, K J *J exp Med* 1956 104, 193
[13] Rittel, W, Iselin, B Kappeler H, Riniker, B, Schwyzer, R *Helv chim Acta*, 1957, 40, 614
[14] Bumpus F M, Schwarz, H, Page, I H *Circulation*, 1958, 17, 664
[15] Wakerlin, G C *ibid* p 653
[16] Skeggs, L T, Kahn J R *ibid* p 659
[17] Blacket, R B Depoorter, A Pickering, G W, Sellers, A M, Wilson, G M *Clin Sci* 1950, 9 223
[18] Byrom, F B, Dodson, L F *ibid* 1949, 8, 1
[19] Harrison, T R, Grollman, A, Williams, J R *Amer J Physiol* 1940, 128, 716
[20] Wilson, C, Byrom, F B *Quart J Med* 1941, 10, 65
[21] Mackaness, G B, Dodson, L F *Brit J exp Path* 1957, 38, 628
[22] Dodson, L F *ibid* p 635

To turn to a more fundamental question Is essential hypertension a form of renal hypertension? **Goldblatt**'s experiment was designed to test the hypothesis that the structural arterial changes observed at necropsy were not the result but the cause of the hypertension, and he has always maintained that his results provide general support for the hypothesis Renal and essential hypertension resemble one another very closely in many respects, as **Goldblatt** points out [4], and this certainly suggests that a common mechanism may be at work Moreover, there is recent evidence that the hypertensin content of human blood is raised slightly in benign hypertension and very greatly in malignant hypertension [16] Nevertheless there is singularly little evidence either from biopsy or postmortem material that mild or early essential hypertension is attended by structural disease of the renal arteries Almost all workers therefore regard the arterial lesions observed at necropsy as secondary to the hypertension, and hold that any primary narrowing of the arterial bed must be functional The distinction is important, because while increased tone of the renal arterial tree is potentially reversible organic narrowing is certainly not

If essential hypertension is in fact renal in origin—and conclusive evidence is still lacking—the most important outstanding problem will be to find out the cause or causes of the increase in renal arterial tone

Metals and Plastics in Intraocular Surgery

Ophthalmic surgeons have been keenly exploring the potentialities of implanted inert materials, especially plastics—notably for the purpose of correcting refractive errors by means of intraocular artificial lenses **Harold Ridley**, the first in this field, in 1951 described his method for overcoming the visual defect in cases of aphakia by means of an acrylic lens inserted behind the iris and in front of an intact posterior-lens capsule [1 2] By 1953, however, it was evident that this technique had its limitations The artificial lens had to be inserted at the same time as an extracapsular cataract extraction was performed so that there was no means of checking the aphakic correction before the implant was inserted, and furthermore patients in whom the posterior capsule had been divided or had been removed were not eligible Perceiving the possibilities of this technique, other workers, including **Strampelli** [3] in Italy, **Schreck** [4] in Germany, and **Barraquer Moner** [5] in Spain, evolved an implant placed in front of the iris and behind the cornea, with feet wedged in the anterior-chamber angles and carrying a central optical portion, the correction of which could be modified to suit the requirements of the individual case An important advantage of the anterior-chamber implant is that it can, and indeed should, be inserted after cataract surgery has been completed, thus enabling the surgeon to minimise the operative trauma to the eye at each session Trauma to the eye has been further reduced by the introduction of new methods of sterilising the implants While polymethyl methacrylate (or "acrylic") is completely inert in the tissues, with the original method of sterilisation by cetrimide small quantities of this irritant were adsorbed by the implant, subsequently leaking out into and irritating the eye Sterilisation by ultraviolet light is open to the objection that it degrades the parent chemical, producing an irritant monomer near the surface of the implant, which would have the same effect as cetrimide **Frederick Ridley** [6] has devised a simple and effective method of sterilising acrylic implants with 10% sodium hydroxide

Uniocular cataract and uniocular aphakia are by no means rare The disability in such cases is considerable, unaided vision is usually less than 3/60, and the patient is denied binocular vision In children especially, the useless eye will tend to converge or diverge, and an ugly squint-combines with a functionless eye to give the patient a sense of inferiority which may produce serious psychological trauma Attempts to use a normal eye with an aphakic one by means of spectacles fail because of aniseikonia amounting to about 30% A contact lens for the aphakic eye will reduce the disparity in image size to about 10%, but many patients cannot tolerate even this amount of aniseikonia An anterior-chamber implant reduces the figure to about 3–5%, which is tolerable

At this year's Oxford Ophthalmological Congress, **Choyce** [7] described 60 cases of uniocular aphakia treated with acrylic anterior-chamber implants He stressed that cataract surgery must be completed at least six weeks before implantation is undertaken In most of **Choyce**'s cases binocular vision was restored and in the remainder alternating suppression developed, accordingly diplopia was not experienced even by patients who had previously had diplopia with a contact lens About a third of his cases had resulted from trauma, and the length of time which had elapsed since the injury was of no consequence, 6/6 vision was restored to some patients as long as fifty years after injury had caused a cataract If the injury had occurred in early childhood amblyopia ex anopsia was inevitable, and limited the visual result, but patients appreciated the restoration of even slight unaided vision to what they had come to regard as a useless eye Another third of **Choyce**'s cases were of uniocular senile cataract in patients over 50 years of age, and after operation these too had the use of the two eyes together, instead of having to decide which eye to use The remaining patients had either heterochromic cyclitis (all did well) or congenital uniocular cataract (some did well) It is only two years since the first implantation in this series, and it remains to be seen whether **Choyce**'s results stand the test of time and are confirmed by other surgeons, but it seems likely that the problem of the patient with uniocular aphakia who cannot tolerate a contact lens has been solved

Theoretically, anterior-chamber implants can be put to other uses—for example, the correction of high

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[1] Ridley, H *Trans ophthal Soc U K* 1951, 71, 617
[2] Ridley H *St Thomas's Hosp Rep* 1951 7, 12.
[3] Strampelli B *Ann oftal clin Ocul* 1954, 80, 75
[4] Schreck, E *Ber dtsch ophth Ges* 1955, 59 212
[5] Barraquer Moner, J *Estud inform Oftal*, *Barcelona*, 1954, chapt 15, p 6
[6] Ridley, F *Brit J Ophthal* 1957, 41, 359
[7] Choyce, D P *Trans ophthal Soc U K* (in the press)

myopia and other refractive errors in phakic eyes An opaque implant could be used to enforce occlusion of the good eye in a squinting child who would not tolerate ordinary methods of occlusion—and, after all, removal of these implants is simple But merely opening the eye, let alone inserting so large a foreign body, must substantially increase the chances of the lens becoming cataractous, and at present there is no justification for inserting anterior-chamber implants into eyes which retain their own crystalline lenses In cases of glaucoma fistulising operations are usually successful in White patients In the Negro they almost always fail, and much work has been done, especially by STONE et al[8] in the U S.A., on the use of polyethylene wicks and tubes and of tantalum wire Efforts to replace vitreous by non-living materials have not so far been successful, transfer of human vitreous seems to offer the best prospect of success at present.[9-11]

The possibility of burying implants incompletely within the eyeball has been closely studied in rabbits by STONE et al[12] in their search for an artificial cornea Edge-to-edge union between cornea and acrylic cannot be induced, but if the cornea is split from limbus to limbus, just superficial to Descemet's membrane, an acrylic disc can be slid into this interlamellar space. These discs are well tolerated, later a smaller disc of overlying cornea can be removed by trephining, and still later a similar posterior disc removed via the anterior chamber Such an opening will remain patent until the natural death of the animal This ingenious technique provides an opportunity to study the reaction of the corneal cells to incompletely buried acrylic but clinically it is not likely to replace the use of human donor material for cases requiring conventional lamellar or full-thickness keratoplasties Nevertheless TUDOR THOMAS[13] has described a penetrating acrylic implant retained in place by an overlying lamellar corneal graft, and has by this means been able to help patients whose eye condition was extremely unfavourable for ordinary methods of corneal transplantation

What Hospitals for Children?

Professor ILLINGWORTH's article this week shows once more how much care and thought are needed if the child in hospital is to be treated as he should be Can anyone reading it be satisfied with a system in which many children are still looked after by hospital doctors and nurses to whom pædiatrics is a sideline? Reacting not unreasonably from the trend towards making everything a specialty, some physicians and surgeons would defend their right to go on treating both old and young, even side by side, and of course it is true that skill with the one phase of life does not exclude skill with the other But the child is not just a small adult, his management unquestionably requires both special study and special experience, and when he is seriously ill his survival may depend on treatment by a team which is fully accustomed to some technique peculiar to his age. (The treatment of œsophageal atresia in the newborn, described by Dr HELLINGS and her colleagues on p 182, is a case in point.) Whenever his disease is complex or difficult, the child will have a better chance if the doctor in charge of him is in a position to get help from surgeons, pathologists, radiologists, and other specialists who have given much attention to the pædiatric side of their specialty and have come to think in terms of children

One essential, then, is a staff which, at all levels and in all departments, is (as the Royal College of Physicians[1] put it) "attuned to the special needs of the sick child", and the other is a staff large enough to include all the necessary talents Both these conditions can be fulfilled in a special children's hospital, or in a big children's block forming part of a general hospital, but they are not fulfilled in most of the hospitals up and down the country to which so many children are admitted From the medical standpoint, only the large pædiatric unit can be fully efficient, and, if there is a surplus of children's beds, it is the small units in general hospitals that should be eliminated—not the children's hospitals Some of the latter, though they appear relatively small and inconvenient to the administrator, are relatively large and convenient for the children, and until a hospital authority can provide something equally large and convenient, *for children*, as part of a general hospital, it should leave them alone—or try to strengthen them

As things are today, pædiatricians who have beds in both kinds of hospital not uncommonly transfer patients from the general hospital (sometimes a teaching one) to the children's hospital They do this because, for a difficult case, they regard the children's hospital as better—better perhaps for consultation, better for investigation, or better for treatment. In a hospital treating children only, all the departments are adapted specifically to their needs For instance, whereas the laboratory of a general hospital might ask for 5 ml of blood from a vein, in a children's hospital the investigation would be done on 0 5 ml of blood from a heel prick. Again, radiography of the lungs in a general hospital often produces a useless result, the wriggling baby being askew and the film lacking definition (All too often, moreover, the whole baby is unnecessarily exposed to X rays) As a rule, the films produced in a children's hospital, by those who are used to handling the very young, are much superior For treatment, the children's hospital will have teams for managing neonatal obstruction, acute gastroenteritis, metabolic disturbances, and the many other emergencies so difficult to cope with in the absence of an experienced team

Even the everyday nursing of children demands technique and methods quite different from those used for adults, and, as the Royal College of Physicians emphasised, the training for it must be correspondingly specialised In providing such training the children's hospitals have their own kind of success Thus a pædiatrician with beds in a teaching hospital, and also in the children's hospital attached to it, remarked that, though the parent undergraduate hospital attracts students of better education, the nursing care of children is very much better at the children's hospital—the explanation being that the young women there have taken up this work because they particularly want to do it Both the children's hospitals and the larger pædiatric units in general hospitals could usefully give three months' training to many student nurses working for the general register, but only on condition that they have enough fully trained pædiatric nurses to give the teaching, and that the students are regarded for the most part as supernumeraries For such students, doing their general training, a small and poorly staffed children's unit in a general hospital where the handling of children is unsatisfactory affords experience which is rather worse than useless

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[8] Stone W New Engl J Med 1958 258, 486, 596
[9] Shafer, D M N Y St J Med 1956, 56, 3300
[10] [illegible], P McG Trans ophthal Soc U.K. 1957 57, 61
[11] Sharland C D ibid p 69
[12] Stone W, Jr, Herbert, E. Amer J Ophthal 1953, 36, 169, ibid 1955, 39 185
[13] Thomas J W T Trans ophthal Soc U.K 1955, 55, 473

[1] Children in Hospital Report approved in comitia by the Royal College of Physicians of London and published in The Lancet, 1957, i, 926.

The reasons why there is less demand on children's beds than in 1948 are (1) the physical health of children has improved, (2) their illnesses are often shortened by more effective treatment, (3) probably more of them are treated at home, (4) additional children's wards have been opened in general hospitals, and (5) many children who would previously have gone into children's hospitals and general hospitals now go into fever hospitals—where there are always empty beds We have no recent figures for the distribution of child patients, and in particular we do not know how many are in adult wards, but the returns of one regional board for a day in the autumn of 1955 showed that of the 1568 in children's wards 1082 were " medical ", and that only a little over half of these were under the care of a pædiatrician Of the other 532 medical cases 243 were in fever hospitals Because admission is easy, children nowadays go to such hospitals with pneumonia, meningitis, septicæmia, gastroenteritis, and rheumatism, not to mention a good many undiagnosed conditions ranging from cœliac disease to congenital hæmolytic anæmia Sometimes, of course, the child thus admitted finds medical and nursing care which is fully equal to the occasion, and this journal, like others, has recorded fine work for children which has been done in fever hospitals—as also elsewhere—by physicians who would neither claim to be pædiatricians nor wish to limit themselves by such a title On the other hand, many fever hospitals—including some of the large ones, have poor facilities (e g , in pathology), insufficient nurses, and no arrangements for educating the children while they are in hospital or for following them up when they have left and some of the smaller ones have no resident medical staff To the hard-pressed family doctor, anxious about his young patient, such a hospital's willingness to accept the case has often been a godsend , and very often, as we have said, excellent care has been given despite all the difficulties But the development of fever hospitals as supplementary children's hospitals can scarcely be defended now that there are said to be too many children's beds and some of the children's hospitals are themselves faced with closure Instead of making fever hospitals responsible for children with non-infectious diseases, it would be better to make children's hospitals and general hospitals responsible for fevers—equipping them with units for the purpose, as has been done in the U S A and many Continental countries

In the region we have mentioned, 28 of the hospitals which had children's beds (medical, surgical, ear, nose, and throat) had fewer than 15, and we do not believe that a number like this, or anything like it, permits the formation of a pædiatric group or environment capable of giving the varied yet specialised care that children so often require If the treatment of sick children is to improve, the policy should be not only to discontinue the routine admission of children to adult wards but also to eliminate, progressively, the children's units which are too small to be pædiatrically viable On the positive side, support should be given to the larger units—children's hospitals and big departments in general hospitals The Ministry of Health would set the ball rolling in the right direction if it officially endorsed and made known to administrative bodies the report of the Royal College of Physicians committee,[1] on which it was represented A circular to regional boards could emphasise

1 The need to build up, in each region, a relatively small number of big pædiatric units, fully staffed and fully equipped —with special attention to any children's hospitals, from which will come much of the pædiatric staff of the future As the college suggests, branch outpatient pædiatric departments can be based on these units

2 The need to discontinue the use of fever hospitals for children not suffering from the so-called infectious fevers, to link the fever hospitals with pædiatric hospitals or units,[2] and to arrange eventually for the treatment of these fevers in isolation wards forming part of children's hospitals and general hospitals

3 The need to stop indiscriminate admission of children to adult wards

Where there are more children's beds than an area can use, the units to be closed should be those that are too small to give the special kind of care, the special skills, and the special knowledge which children require —and to which they are entitled no less than adults

Poliomyelitis Vaccination

THE Government's programme of vaccination against poliomyelitis is to be extended from the present age-limit of 15 to 25, a wider range of hospital staff and their families are to be included, and a start is to be made with third injections of people already vaccinated twice This was announced by Mr DEREK WALKER-SMITH in the House of Commons on Monday Those hitherto eligible for vaccination are children born in 1943-57, expectant mothers, general practitioners, and hospital and ambulance staffs and their families At June 30 a total of 6,570,157 had registered, of whom 4,481,837 had received two doses and 856,388 one dose, 1,231,932 were awaiting vaccination The registration-rate for children under 15 at June 30 was 53 6% The number of doses needed to complete registrations was 3,320,252, and 3,766,651 doses were held by local health authorities Of the new groups those aged 15-24 total some 6,250,000 and hospital staffs and families 500,000, and those eligible up to March 31, 1959, for a third injection may total 6,500,000 It is proposed to ask local health authorities to offer as soon as possible third injections to children vaccinated in 1956—about 200,000

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[2] Ministry of Health circular R H B (48) 1

Annotations

THE PRINCESS LOUISE

THE Minister has at last said what he now thinks should be done with the Princess Louise (Kensington) Hospital for Children: it should be cut in half, so that the present staff have two wards for pædiatrics while St. Mary's Hospital have the other two for obstetrics and gynæcology. Let us hope that this judgment, like Solomon's, is intended merely to reveal the relative strength of the affections of the claimants, for otherwise it has few merits. True, the division, unlike that of Solomon's baby, is to be temporary, and a couple of years will give time for reflection. But after these years, unfortunately, the hospital, as a children's hospital, may be virtually dead. If we are right in the arguments of our preceding article, the Minister is wrong in reducing a children's hospital of 76 beds to a mixed hospital with less than 40 children's beds. If he thinks that there are too many such beds in the area, the correct policy is to eliminate one or more of the smaller units in general hospitals which cannot give children the full benefit of pædiatric knowledge and training.

The Princess Louise Hospital was built in 1928, at a cost of £75,000 raised mainly within the borough, to meet the needs of the rapidly developing and overcrowded area of North Kensington. In 1945 its board decided that, under a National Health Service, its security, wellbeing, and development would be best secured by joining a teaching hospital, and in 1946 it amalgamated with St. Mary's on the understanding (we are told) that it should retain its name and continue as a children's hospital. About the same time St. Mary's also amalgamated with the Paddington Green Children's Hospital, and ever since then they have had more pædiatric beds than they need for teaching, and fewer beds of other kinds.

Their first proposal in 1949 was to convert their smaller children's hospital (Paddington Green) into a hospital for adults, but this was strongly opposed in the neighbourhood, and since 1955 they have concentrated on the conversion of the Princess Louise, which is thought to be architecturally easier. This, too, aroused opposition, and in November, 1956, the Minister is said to have accepted a solution whereby St. Mary's should allow the Princess Louise to be transferred, as a children's hospital, to the North West Metropolitan Regional Hospital Board, accepting in exchange additional adult beds for teaching purposes in Paddington General or St. Charles' Hospitals. But St. Mary's refused to do this because they rightly wanted their teaching beds to be directly under their own control.

The Minister's new solution of the problem is to allow St. Mary's "to convert two wards at the Princess Louise Hospital for the temporary use of maternity patients pending the provision of the professorial unit [in obstetrics and gynæcology] at St. Mary's Hospital, and to defer a decision on the long term future of Princess Louise Hospital until that unit is nearing completion." He is "satisfied that it is practicable for those entitled to avail themselves of the benefit of the objects of the Princess Louise Hospital for Children to enjoy similar facilities in suitable neighbouring hospitals."

If the Princess Louise Hospital were consistently empty, while units in neighbouring hospitals were full, there would be a case for saying that it is no longer doing its work and can suitably be spared. But that does not seem to be so.

Because of the seasonal fluctuations in demand, bed-occupancy in children's hospitals over the twelve months is bound to be relatively low, and at the Princess Louise admissions were curtailed in 1955 and 1956 by poliomyelitis and throughout 1957 by a *Salmonella typhi-murium* infection. Even so, the following figures are not unsatisfactory:

	Inpatients	*Bed occupancy* %
1946	832	68
1947	939	63
1948	1088	70
1949	1020	75
1950	1211	78
1951	1427	69
1952	1656	71
1953	1758	80
1954	1807	76
1955	1363	75
1956	1726	73
1957	1290	58

Recent uncertainties have already weakened the staff because a number of consultant and other medical vacancies have not been filled, and of course this weakening would continue if the Minister's proposal were fulfilled. But the hospital remains, pædiatrically, in a stronger position than many smaller units. The general-purposes committee of the Kensington Borough Council, which is vigorously opposed to the proposal, refers as follows to grave illness treated in the hospital[1] last winter:

> "We . . . are convinced the Princess Louise Hospital, truncated by the threatened loss of two whole wards, cannot adequately meet the continuing and indeed growing needs of the child population of the area, still less cope with an epidemic such as the recent virulent and rapidly fatal chest complaint in infants known as bronchiolitis. This recent outbreak called for the use of every available cot and bed and at one stage as many as sixteen infants were in oxygen tents at the same time."

The Kensington committee appeals to the Minister to revert to what apparently was his previous plan—namely, that the Princess Louise should be preserved as a children's hospital and be placed (as though its unfortunate amalgamation with St. Mary's had never taken place) under the North-West Metropolitan Regional Hospital Board—or alternatively asks him to attach it to one of the teaching hospitals which has a deficiency rather than a surplus of children's beds. The Minister could scarcely wish to oppose this suggestion if St. Mary's could be induced to make it, and St. Mary's would surely be wise to rid themselves of what has clearly become a very embarrassing problem. To do so they must obtain elsewhere, for a time, the obstetrical and gynæcological beds they will need while their new unit is being built, but, according to the Kensington committee, the regional board is prepared to find these, "possibly by closing the children's beds at St. Charles'," which is close beside the Princess Louise. We hope that, if St. Mary's can count on controlling the borrowed beds, this alternative may prove acceptable.

ANOMALOUS AIR SHADOWS

LUMBAR air encephalography by a technique designed not to alter the intracranial pressure is being increasingly used, as an alternative to ventriculography, in the investigation of intracranial tumours, including those in the posterior fossa.[2] When there is obstruction to the cerebrospinal-fluid pathways, air filling of the ventricles may not take place and the interpretation of the films depends largely on the appearances of the basal cisterns and cerebral sulci. Schechter et al.[3] have reported from the National Hospital, Queen Square, four cases in which there were surprising air shadows. In all four there was an obstructive lesion in the posterior fossa: in one an astrocytoma invading the fourth ventricle, shown at operation and necropsy, in one an intrinsic tumour of the medulla oblongata demonstrated at operation, and in the other two stenosis of the aquaduct of Sylvius shown by

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1. *Lancet*, 1958, i, 482.
2. Norlén, G., Wickbom, I. *J. Neurol. Neurosurg. Psychiat.* 1958, 21, 1.
3. Schechter, M. M., Bull, J. W. D., Carey, P. *Brit. J. Radiol.* 1958, 31, 317.

ventriculography In all four patients air encephalography showed abnormally large sulci corporis callosi, and in one the cingulate sulcus was also unusually wide and well outlined In the two tumour cases an unusual shadow was seen just to the left of the third ventricle, this shadow was half-moon shaped in the lateral position, and in the anteroposterior view was situated just to the left of the midline, being rounded medially and drawn out laterally Schechter et al thought that this latter shadow represented a dilated cisterna ambiens and confirmed this by studying the radiological appearances of this cistern in a normal brain and in the necropsy specimen of their first case after pledgets of cotton-wool soaked in radio-opaque material had been placed in the cistern

To elucidate these unexpected appearances further, the Queen Square workers reviewed a hundred normal lumbar encephalograms and a hundred encephalograms of patients in whom there was thought to be cerebral atrophy Unfortunately they do not mention any criteria on which the diagnosis of cerebral atrophy had been made In the normal group some filling of the sulci corporis callosi was shown in five cases and of the cisterna ambiens in ninety-two, but never to the same degree as in the two tumour cases In the cases of cerebral atrophy the sulci corporis callosi were seen in ten cases and the cisterna ambiens in ninety-three, but here again considerable dilatation was never seen Pronounced filling of the sulcus corporis callosi on air encephalography has been reported on four previous occasions in cases of tumour of the posterior fossa, and a case has been described [4] in which there was a shadow similar to those ascribed by Schechter et al to dilatation of one side of the cisterna ambiense associated with a posterior-fossa meningioma Schechter et al do not give any convincing explanation of these surprising encephalographic appearances with obstructive lesions in the posterior fossa, but their observations are of considerable practical importance, as it would be easy to ascribe dilated cerebral sulci and a dilated cisterna ambiens to an atrophic process in the brain, and to omit doing further investigations which might reveal a tumour in the posterior fossa

ACUTE EPIGLOTTITIS

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4 Castellano, F , Ruggiero, G *Acta radiol , Stockh* 1953, suppl 104
5 Jones, H M , Camps F E *Practitioner*, 1957, 178, 223
6 Berenberg, W , Kevy, S *New Engl J Med* 1958, 258, 870

Special Articles

COMMUNITY TREATMENT OF MENTAL ILLNESS *

DUNCAN MACMILLAN
M D , B Sc Edin , F R C P E , D Psych
PHYSICIAN-SUPERINTENDENT,
MAPPERLEY HOSPITAL, NOTTINGHAM

THE isolation of the mental hospital, which was practically absolute before the Mental Treatment Act of 1930, is rapidly disappearing, and more and more psychiatric patients are being treated in the community instead of in the hospital The hospital's first link with the community was the outpatient department Later liaison was gradually established with outside services such as probation departments, industrial medical officers, child-guidance centres, and the Ministry of Labour Social psychiatry continued to grow steadily, but of late years the pace has quickened as more and more community centres, day hospitals, and night hospitals have been opened These have varied in form and setting Some are independent, while some are associated with mental hospitals and some with psychiatric units in general hospitals Some offer domiciliary visits, some do not

PARTIAL COMMUNITY CARE

All these developments are in fact extensions of the work of the outpatient department The day hospital offers a more comprehensive system of aftercare which enables the inpatient to be discharged from hospital earlier and often avoids the need for readmission, while the night hospital is a useful halfway stage where patients can adjust themselves gradually to life and work in the community Day centres and day hospitals offer an alternative to hospital treatment as well as sometimes preventing the need for it, and their group atmosphere is of inestimable value for certain patients They are useful additions to hospital resources and lessen the strain on beds, but they do not necessarily alter the function of the hospital

Other schemes try to relieve the pressure on mental-hospital beds more directly In Amsterdam, for instance, there is a scheme for domiciliary visits and community care run by the city authorities[1] In this country, efforts are being made in different ways It is sometimes said that a community service is only practicable in a compact urban population, but the Worthing[2] experiment shows what can be done in a county area

Though these schemes were usually started with the idea of saving money and hospital beds, experience shows that they have other advantages, and that they allow the patient to be helped in ways outside the scope of inpatient treatment Earlier treatment, prophylactic measures, adjustment of interpersonal relationships, and treatment of the family as a unit all become possible

Most of the community schemes do not cope with all forms of psychiatric illness For instance, patients with chronic psychoses, particularly if they have antisocial reactions, are usually sent to the local mental hospital and pass from the care of the community service Some schemes are more comprehensive, but generally speaking the chronic mental patient is excluded from community treatment once the home situation becomes too strained for him to go on living at home

A Comprehensive Service

The system of community treatment which I believe offers patients the best care at all stages of their illness is a comprehensive service which treats all mental illness, including the chronic psychoses This means that the mental hospital must take an active part in the scheme and is the most practical way of using our existing resources It also means that we must alter our attitude to the chronic patients, and establish a personal relationship with them

In a service of this kind admission to hospital is not restricted It is still promptly available, but it is limited to short-term episodes in a course of treatment which is based on the home Admission and discharge are arranged in a flexible way with a minimum of formality The function of the hospital is altered and modified, so that it becomes only one part, but an essential part, of the service The resources and energies which would otherwise be spent providing long-term residential accommodation for patients can be diverted to domiciliary and community activities The emphasis in the scheme of therapy moves from the hospital to the home, with community treatment playing an important part in all psychiatric illnesses The patient retains his social and economic independence, and the mental hospital, like the general hospital, offers him specialised inpatient treatment when the resources of the home and the domiciliary and community services become temporarily unable to cope with his illness

There is a tendency to regard long-continued hospital treatment as the only possible course in severe long-term psychoses There is a fear that without it antisocial acts would increase, and many people are doubtful how the patient would respond to community influences Yet the aggression of the psychotic is due to psychological insecurity, and is secondary to the primary reactions of apprehension, depression, or suspicion Early help with his emotional upsets, and a personal relationship in which he feels that his problems are understood are effective means of reassuring him and easing emotional tensions To restrict such a patient, on the other hand, is the very way to aggravate his emotional disturbance He will tend to become confirmed in his feelings of suspicion, depression, or apprehension, and his tendency to antisocial acts may be increased It would accordingly seem sensible on psychiatric grounds to substitute for long-continued custodial precautions the establishment of a personal relationship with the patient

THE HOSPITAL'S ROLE

For a comprehensive scheme to be successful the following conditions are essential integration of the hospital service with the local health authority, removal of barriers isolating the hospital from the community, an internal psychotherapeutic atmosphere in the hospital, and an enlightened and informed public opinion in the community

Integration of Hospital and Local-authority Services

This may be arranged by various administrative procedures Nottingham, for instance, has a "joint user" arrangement, under section 51 of the National Health Service Act, which enables the medical staff of the mental hospital to act also as the medical staff of the mental-health department of the local health authority[3] At York, without formal referral to the ventriculography In all four patients air encephalography showed abnormally large sulci corporis callosi, and in one the cingulate sulcus was also unusually wide and well outlined In the two tumour cases an unusual shadow was seen just to the left of the third ventricle, this shadow was half-moon shaped in the lateral position, and in the anteroposterior view was situated just to the left of the midline, being rounded medially and drawn out laterally Schechter et al thought that this latter shadow represented a dilated cisterna ambiens and confirmed this by studying the radiological appearances of this cistern in a normal brain and in the necropsy specimen of their first case after pledgets of cotton-wool soaked in radio-opaque material had been placed in the cistern

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* Based on a Maudsley lecture given to the Royal Medico-Psychological Association on Feb 10, 1958

[1] Ling, T M *Lancet* 1954, i, 1127

[2] Carse, J , Panton, N , Watt, A *ibid* 1958, i 39

[3] Macmillan, D *ibid* 1956, ii, 1094

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Deterioration through loneliness is common, and here we find the group atmosphere of the day occupation centre invaluable The health visitors are now reporting deaths which leave an old person living in solitude, so that arrangements may be made for them to attend the centre as a preventive measure Attendance at the centre is also useful for patients who are partially rejected by their relatives and who relapse after improvement in hospital Such patients are now introduced to the centre immediately on discharge

Because of this policy of prompt admission for a limited number of weeks, the number of geriatric admissions increased at Mapperley Hospital from 202 in 1951 to 439 in 1956 But the number of patients admitted during 1951 who were still in hospital four months after the end of the twelve months' period was 41, while the corresponding number for 1956 was 49 The geriatric inpatient wards are thus coping with many more patients without extra beds The old people are happier, and the relatives have their guilt reactions resolved, and are helped to solve their emotional conflicts We have also been able often to take preventive action through our opportunities of studying the evolution of the emotional situations and of personal relationships within the family

Where the strain on the relatives is too great, whether for physical or (more commonly) psychiatric reasons, we accept responsibility and provide a bed in the long-stay annexe Arrangements have been made for transfer of long-stay patients on an exchange basis with the geriatric wards of the general hospital or with the residential accommodation of the local-authority welfare services department This provides a method of improved classification and ensures that beds are promptly available

Schizophrenia

Patients with chronic schizophrenia and paraphrenia form a large proportion of the long-term inmates of mental hospitals They are inclined to be more uncooperative and reluctant to accept help than other psychotic patients, and their delusions may make them antisocial and resentful Compulsory short-term orders for three or seventeen days may be needed at first. Active treatment is given immediately on admission, and by the time the order ends they are usually prepared to finish their treatment as voluntary patients After discharge contact is maintained through the social worker and the aftercare clinic The patients are helped with work problems, and help is given if necessary with the home situation If they relapse or the home situation becomes too strained, readmission is arranged—again by short-term order if necessary After repeated admissions social adjustment is usually achieved If a repeated seventeen-day period proves ineffective, use of a twenty-eight day period usually is beneficial

This procedure demands much effort from the psychiatrist and social worker and high degree of cooperation from the relatives Occasionally one is just reaching the stage of feeling that a losing battle is being fought, when the attitude of the patient gradually alters and he begins to cooperate and improve Communication with schizophrenics is difficult, and on their part is effected at first through symbols Improvement is so slow as to be almost imperceptible They respond gradually and steadily to measures which maintain their self-esteem and enable them to readjust socially

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Discussion

There is a tendency to regard preoccupation with the setting in which the patient receives treatment as subsidiary to actual measures of treatment I submit that the provision of a mental health service in which the patient can be treated without disturbance of his self-respect and which preserves the essentials of the doctor-patient relationship is in itself a psychotherapeutic measure of fundamental importance The patient's self-confidence is almost always disturbed, he is emotionally upset, and needs the help of a community service even more than other patients Restriction in hospital and deprivation of civil rights undermine further his self-confidence and aggravate his emotional disturbance

Family relationships and community relationships are often seriously upset by the time a patient is brought to our notice, and a tremendous strain is imposed on a family when one member is mentally ill To treat a psychosis without dealing with such disturbed relationships is to invite subsequent relapse Prolonged removal of the patient from the family tends to make the family close its ranks and resist later attempts to restore him to their midst Many patients remain in our mental hospitals though their difficulties are no longer psychiatric but social

Often a faulty relationship with another member of the family has been one of the causes of the patient's illness, and adjustment of the attitude of this relative may be as important as the treatment of the patient These relationships in the home, at work, and in the community can be adequately dealt with only by community methods, and with a due appreciation of the need for adjustment of the attitude of the other people concerned

The mental hospital segregates people in artificial large groups It is suitable for short-term treatment and rehabilitation, but not for long-term social adjustment For this we are dependent on the family, which is accustomed to dealing with its own relationships The family group, if not disrupted and interfered with, usually

Ministry of Health, the local mental hospital is linked with the local health authority of the city At Oldham the regional hospital board and local-authority services have been integrated without incorporating the mental hospitals Good relations between medical superintendents and medical officers of health are also creating a large measure of cooperation in other areas of the country on a more informal basis

Barriers between the Hospital and the Community

The main barriers are the locked-door system and the custodial duties of the hospital The open-door principle must be established before the hospital can be accepted by the community Another barrier is certification, which segregates all those to whom it is applied from other human beings The stigma and the deprivation of civil rights cause resentment in the mind of the patient which may last many years Certification also has an adverse effect on the relationship between the patient and his relatives, his friends, and other members of the community, because it leads them to regard him as a person apart and different from themselves With modern resources in therapy, compulsion can be limited to brief periods, and arrangements made for the patient to complete his stay in hospital on a voluntary or non-statutory basis Even the voluntary formality is resented and patients' appreciate the non-statutory procedure

The Hospital's Psychotherapeutic Atmosphere

The role of the hospital in a community treatment scheme is to prepare the patient for life in the outside world again Its wards should be psychiatric rehabilitation units each with its own group atmosphere This necessitates a complete change of attitude in the staff But no true doctor-patient or nurse-patient relationship can develop so long as one party is a prisoner of the other and legally inferior to the other When the doors are open and legal disability has been removed, the staff use their personalities to deal with psychiatric crises and to help the patient to solve his problems of adjustment A happy relationship develops, and the staff (medical, nursing, and social) join with the patient to explore methods of preparing for his return to the community

Opening the doors and removal of certification are essential preliminary measures, but overcrowding must also be dealt with, so that the patient can receive adequate individual attention Community treatment makes this easier by enabling the admission units to cope with the reduced demands made on them, without having to move patients into other wards to make room for fresh admissions Accommodation for patients is not lavish and is inadequate for active rehabilitation

Many other measures, such as modernisation of ancient buildings and furnishings, more individual amenities, and the division of the patients into smaller groups, are also needed Occupational therapy is essential The patient should graduate from the occupational-therapy class to employment in the hospital departments, later to an industrial rehabilitation unit, and finally to work in the community while still living in the hospital under a "hostel" or "night hospital" scheme

Education of the Community

The attitude of the community to mental illness and to the mental hospital must be altered before there can be willing and early acceptance of psychiatric treatment by the patient The hospital and local-authority staff can lead the way, but the gap between the attitude of the public and that of the medical, nursing, and social staff should not be too great One of the first essentials in lessening the gap is an internal hospital community atmosphere in harmony with accepted standards of social behaviour, which does not offend the susceptibilities of the public when they visit the hospital A community does not accept a hospital until the patients on their return home speak with appreciation of their experience in hospital Education by lectures and other means is necessary, but is not really effective unless backed by visits to all wards and departments of the hospital where the public may see for themselves the conditions under which the patients are treated

An improved attitude to the hospital gradually leads to a more enlightened attitude to mental illness in general, and this influences the attitude of the patient to his illness He seeks treatment earlier, and is more cooperative because he is less apprehensive, and is willing to accept the help of the mental hospital as if it were a general hospital The patient is also influenced by the atmosphere of the hospital, and the staff of the admission wards believe that the most important factor in gaining the cooperation of the short-term compulsory patient is the attitude of the other patients The viewpoint of the patient, the atmosphere of the hospital, and the attitude of the community all need adjustment, but once the change has begun, each reacts beneficially on the others This enables an effective liaison to be made with employment exchanges, local employers, industrial rehabilitation units, probation departments, and all the other agencies in the community whose help the patient is likely to need Once this stage has been reached, the help given by a "league of friends" can be invaluable

WHAT CAN BE DONE AT HOME

The home visits in a community scheme of treatment may be made by social workers, by psychiatrists, or by both The visits by the psychiatrist in a service which is integrated with the mental hospital are made at the request of the mental-health department, and are in addition to domiciliary consultations at the request of the general practitioner In the Dutch scheme the first visit is made by a psychiatrist, but our experience at Nottingham suggests that there are advantages in having the first visit paid by a social worker Often the initial investigations and the early visits take much time In some cases a social worker can deal with the patient's social problems and, if need be, refer him to the outpatient department In others the psychiatrist and the social worker pay a joint visit after the preliminary investigations have been completed

TWO PRACTICAL EXAMPLES

Senile psychosis and schizophrenia are two illnesses which fill many hospital beds and cause overcrowding of hospital wards To illustrate the use of community treatment methods as an alternative to long-term or permanent inpatient stay I shall describe the procedures we use with these two psychoses at Nottingham

Senile Psychosis

When a patient aged 65 or over is reported to the mental health department of the local health authority, a domiciliary visit is arranged by a psychiatrist and a social worker They assess the home situation and decide whether the problem is primarily psychiatric, physical, or social If it is psychiatric, they decide whether the patient can be cared for in the community or needs admission to hospital If community care is chosen, the social worker gets in touch with relatives, arranges for home help, informs health visitors or the welfare services department, and takes all other necessary action Attendance at the day occupational centre is arranged when this is thought appropriate and helpful

If admission to hospital is necessary, it is explained to the patient and to the relatives that admission is for four weeks only The cooperation of the old person is obtained, and reassurance is given that there is no question of his being "put away" The relatives are assured that further help will be forthcoming when needed and that no undue burden will be placed on them, but that they must play their part and continue to accept responsibility for the old person In these general discussions with the relatives and the old person we try to show them the situation as a shared problem, to the solution of which all, including the psychiatrist and the social worker, must contribute Short admissions are now being arranged at an earlier stage of the illness, when the relatives first begin to resent the strain of looking after the old person, and before personal relationships have broken down Relief for holiday periods is arranged some months beforehand, so that the family are able to make definite arrangements to enjoy an annual rest from their responsibility of looking after the old person This is particularly important when there are young children in the household

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Family relationships and community relationships are often seriously upset by the time a patient is brought to our notice, and a tremendous strain is imposed on a family when one member is mentally ill To treat a psychosis without dealing with such disturbed relationships is to invite subsequent relapse Prolonged removal of the patient from the family tends to make the family close its ranks and resist later attempts to restore him to their midst Many patients remain in our mental hospitals though their difficulties are no longer psychiatric but social

Often a faulty relationship with another member of the family has been one of the causes of the patient's illness, and adjustment of the attitude of this relative may be as important as the treatment of the patient These relationships in the home, at work, and in the community can be adequately dealt with only by community methods, and with a due appreciation of the need for adjustment of the attitude of the other people concerned

The mental hospital segregates people in artificial large groups It is suitable for short-term treatment and rehabilitation, but not for long-term social adjustment. For this we are dependent on the family, which is accustomed to dealing with its own relationships The family group, if not disrupted and interfered with, usually accepts responsibility for solving its own problems This attitude, if helped and directed into psychotherapeutic channels, can be a powerful rehabilitating factor We should treat the family as the unit—not the patient in isolation

Community treatment averts the development of antisocial attitudes and the overlay of aggression which are produced by compulsion and restrictions, and thus leaves the patients free to deal with their problems of social adjustment Their psychotic symptoms, if fully established, are not eradicated, but they cease to be the major and dominating factor in the patient's existence Compulsory long-term hospital care tends to perpetuate the dominance of the psychosis, whereas the more flexible regime of community treatment encourages the patient's natural tendency to social readjustment and helps him to remain in the community despite the handicap of chronic psychosis

One definite advantage of community treatment is that by means of domiciliary visits psychiatric illness is treated at an even earlier stage than is possible with the outpatient clinic In an integrated mental health service the home and health visitors recognise psychiatric situations before serious symptoms have developed Potential stages of a serious breakdown can be treated, and prophylactic measures started in a way which is impossible without a community service In taking these early steps it is essential to inform the patient's general practitioner, so that he remains a member of the team In Nottingham the system has tightened the links between the mental health service and the general practitioners, who often now refer patients for attendance at the day centre, and for other prophylactic measures, instead of merely referring them for admission

To sum up, community treatment not only makes possible continuity of care for all forms of psychiatric illness but by its beneficial influence on public opinion persuades patients and their relatives to come spontaneously to the mental health department for help and advice, and to accept the mental hospital, like the general hospital, as a place where the patient goes to speed his rehabilitation

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Congresses

STRESS AND MENTAL ILLNESS

In an intense and interesting conference in Oxford last week, some 40 distinguished scientists, predominantly psychiatrists, psychologists, and physiologists, brought together by the Mental Health Research Fund, tackled the subject of "stress" and its action on man's health, particularly the health of his mind They set out to clarify the mass of facts that have sprung in recent years from the growing attack on the questions of how and why the animal reacts to the pressure of its environment in such a bewildering variety of ways People trained in several disciplines, precise and less precise, and often talking therefore in conflicting terms, have contributed to knowledge of the phenomena that this reaction can generate, and the meeting gave prominent thinkers in this branch of biology the chance to illuminate by close contact, often outside the conference room, the difficulties of effectively communicating to one another the observations they have made and the significance they put upon them. Their formal deliberations suggested that it is not yet possible to sketch with confidence an embracing and unifying picture that will include the whole scene. But the gaps that separate the more sharply defined schools of thought—the physiologically minded and those who think in psychological terms, for instance—were not so wide as they at first sight seemed, and some promising bridge-building materials became apparent.

In the report that follows, we can note only a few of the contributions that the conference heard, and the balance between the physiological, the psychiatric, the psychological, the psychosocial must be ill struck, but it is an immediate record of a notable attempt to sum up progress in a subject that may at present defy summing up We hope that the Fund will publish the proceedings in greater detail, prefaced or concluded perhaps by a further analysis and judgment.

WHAT IS STRESS?

In its daunting venture, the conference was fortunate in having as its leader Sir **Geoffrey Vickers**, chairman of the research committee of the Mental Health Research Fund, who was more than equal to the task of giving profitable direction to swiftly changing lines of thought. A prime difficulty, never fully resolved, was to decide what meaning or meanings to attach to the word "stress" Dr **Derek Richter** had prepared for the conference's consideration a concise memorandum on the current usage of this term by different scientists—physicists, biologists, physiologists, psychologists—and ranging from the physicist's precision of dynes per sq cm to the psychologist's "anxiety, tension, or a defensive behavioural response" This helpful document was never formally discussed such a discussion might have served as a clarifying preliminary debate. As it was, everyone understandably adhered to his own notions, without much explanatory definition, and in the early exchanges this was a source of difficulty Sir Geoffrey promptly recognised this nettle and seized it firmly by issuing, on the second morning of the conference, a note on the meanings attached to "stress" during the first day's discussions In this he said

"We require a word to cover all those felt needs which evoke purposeful activity If this be 'stress', then, as Professor Selye says, only death can relieve it To avoid so wide an application, I will use the word 'challenge' to cover both the need and the signal which evokes action to meet it.

"The course of response to these challenges may pass through several stages

(i) The organism can meet the need
(ii) The organism can meet the need but only for a period which may not be sufficient.
(iii) The organism cannot meet the need without abandoning, at least for the time being, the effort to pursue or evade some other relationship
(iv) The organism cannot meet the need at all

"If these stages occur successively the state of the organism will change along four dimensions which are not exactly correlated and all these changes may, in current usage, be attributed to 'stress'

(i) It will change physiologically These changes will depend partly on the energy requirements of the response and partly on its emotional accompaniment. They may begin at stage (i) and often reach their peak in stage (ii) unless they are later complicated by the indirect effect of subsequent stages
(ii) It will change emotionally Anxiety may arise irrationally at stage (i) or rationally at stage (ii) The whole gamut of emotional changes may appear in the course of stages (iii) and (iv)
(iii) It will change behaviourally At the end of stage (ii) its behaviour towards some or all of its other goals will change. At stage (iv) or earlier it will give up its purposeful activity towards the relation which is being defeated
(iv) It will change structurally From the end of stage (ii) it becomes differently structured, as it abandons or modifies one after another of its governing relations"

And he concluded

"To clarify our discussion, I make the following suggestions.

(1) We are concerned with four separate objects of attention, for which we need separate words It is unfortunate that three of these are themselves fourfold.

(i) Four types of (more or less) observable change,
(ii) the situations which cause these changes,
(iii) the processes by which these changes take place,
(iv) the behaviours which accompany these processes

(2) The simplest way, consistent with existing usage, in which we can mark these distinctions, when we want to be precise, is, I suggest, to refer to them as 'stress-change', 'stress-situation', 'stress-process', and 'stress-behaviour'

The terms 'stressor' and 'stress-response' have such strong physiological connotations that they are best reserved for that field, but they would be included by the wider terms 'stress-situation', 'stress-change', and 'stress-behaviour'

(3) Though the four types of change—physiological, emotional, behavioural, and structural—are intimately related, there is clearly not a one-to-one correspondence between them. We should not assume that they are different aspects of the same 'thing', except in so far as we know them to be exactly correlated

(4) The only valid general use of the word 'stress' at present is adjectival It connotes a degree of challenge sufficient to evoke the kind of change or behaviour which interests the particular observer Its meaning therefore depends not only on the 'dimension' in which he is interested but also on the threshold above which appear the kind of phenomena which he finds interesting"

The conference did not achieve a better clarification of terminology than this

MATCHING OF PATTERNS

In his opening remarks, Sir **Geoffrey Vickers** pointed out that disorganisation—or inability to function at one's normal level—might, in fact, be defensive reorganisation exercising a protective role As Field-Marshal Lord Wavell put it, stupidity in generals should never excite surprise, since they were of the few tough enough to be generals at all, their essential qualification being their ability to function at some level in conditions of stress which would cause less stable organisms to break down

The stressful situation which concerned the psychiatrist was produced not by events but by the organism's interpretation of events in relation to itself This in turn was a function of the way in which the individual personality was organised. and any conceptual model of this must include the organisation of experience There accepts responsibility for solving its own problems This attitude, if helped and directed into psychotherapeutic channels, can be a powerful rehabilitating factor We should treat the family as the unit—not the patient in isolation

Community treatment averts the development of antisocial attitudes and the overlay of aggression which are produced by compulsion and restrictions, and thus leaves the patients free to deal with their problems of social adjustment Their psychotic symptoms, if fully established, are not eradicated, but they cease to be the major and dominating factor in the patient's existence Compulsory long-term hospital care tends to perpetuate the dominance of the psychosis, whereas the more flexible regime of community treatment encourages the patient's natural tendency to social readjustment and helps him to remain in the community despite the handicap of chronic psychosis

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Fuller (Bar Harbor, Maine) was particularly interested by the high death-rate in the animals exposed to only a short stress. Could it be that this was the little pebble that started the organism on the non-conformist road, from which it was very hard to turn back?

PRISONERS OF WAR

In the matter of increased mortality in organisms exposed to some form of severe stress, Professor Wolff presented figures derived from a recently completed study of United States prisoners of war. In the late war, 94,000 United States prisoners were taken in Europe and were imprisoned for about ten months. Less than 1% died before liberation. In the Pacific theatre 25,000 Americans became prisoners: they were in prison about four times as long as those captured in Europe and suffered far more threats, abuse, and humiliation. More than a third died before liberation. In the six years after liberation the number of deaths in the Pacific prisoners was more than twice the expected incidence in a similar group not exposed to the hazards of prison camps. The mortality-rate was three times greater in the Pacific than in the European prisoners. Deaths from heart-disease were twice as common, from cancer twice, from gastro-intestinal diseases four times, from suicide twice, from accidents three times, and from pulmonary tuberculosis nine times as common.

STRESS AND EXPERIMENTAL PHYSIOLOGY

To those who found it hard to get a foothold among the psychological and psychiatric concepts of stress and responses to it, Prof. Hans Selye (Montreal) offered the firmer ground of facts gathered in his long study of experimental stress. Inflammation in the limb of a rat caused by the local injection of formalin could be modified by pretreatment with hormones: corticotrophin (A.C.T.H.) inhibited the inflammatory response and somatotrophin (S.T.H.) enhanced it. The intraperitoneal or intravenous injection of egg-white induced an anaphylactic reaction in the rat, and this could be inhibited by stress, but not in the adrenalectomised animal. The changes of periarteritis nodosa could be produced in the rat by administering an anticortisone hormone, such as deoxycortone. Partial ligature of a mesenteric vessel prevented these changes developing in the distribution of that vessel, indicating that the blood-vessels of the hormone-conditioned animal could be damaged by blood-pressures which were of no account in the untreated animal. Cortisone prevented the onset of bone lathyrism in rats fed on a diet that would induce the disease in untreated animals, and conversely S.T.H. would promote severe bone changes in rats eating a diet in which there were only small amounts of lathyrus, amounts that were not previously harmful.

What Professor Selye described as the most important outcome of twenty years' work was the experimental production of cardiac necrosis in rats exposed to corticoid hormones plus immobilisation. A special staining technique identified the areas of muscle susceptible to necrosis by demonstrating early prenecrotic degenerative changes. Potassium and magnesium ions had been shown to prevent these changes. Some aspects of this work have lately been described[1] in these columns.

Professor Selye owned, however, that only a very small part of the reaction to stress was mediated by hormones and by disturbances in the balance of hormone pairs, for, in hypophysectomised animals, the adaption syndrome proceeded much as in the intact animal.

As a supplement to Professor Selye's contribution, Prof. G. W. Harris (London) discussed a possible link between the nervous system and the endocrine glands. The stimulation of neural structures above the hypophysis—in the hypothalamus—evoked changes in target organs similar to those recorded by Selye. The portal system in the pituitary blood-supply suggested that this effect was transmitted by a humoral mechanism.

THE BODILY STRESS RESPONSE

Dr Hudson Hoagland (Shrewsbury, Mass.) described work on urinary metabolites done at the Worcester Foundation for Experimental Biology. The excretion of adrenaline and noradrenaline was measured in ice-hockey players, boxers, and psychiatric patients.

A group of Olympic boxers all had a high adrenaline output (about five times normal) before a fight, the noradrenaline was not raised, except in 2 men who engaged in vigorous shadow boxing before a fight. After the fight, noradrenaline excretion was very high and the adrenaline figures remained high.

Measurements in the Boston Bruins, a tough ice-hockey team, showed a similar pattern. In the 4 players actively skating, noradrenaline output was five to ten times higher after a game, while adrenaline excretion was relatively low. In 2 players "benched" for injuries, adrenaline figures went up while they were watching, and a player who became involved in a fight excreted very large quantities of noradrenaline.

	Noradrenaline (µg per 100 mg	Adrenaline creatinine)
Active players		
Pre-game	2·7	0·36
Post-game	15·3	0·05
Non-players		
Pre-game	2·2	0·23
Post-game	3·3	0·75
Fighting player		
Pre-game	3·5	
Post-game	29·3	

The Bruins coach, evidently a phlegmatic fellow, never showed much response, as judged by excretion of adrenaline and noradrenaline, except as the result of a particularly arduous game with the Montreal team (a finding of which Professor Selye expressed approval).

Anxiety, it could be concluded, was associated with increased adrenaline output, and exercise with a rise in noradrenaline excretion. Similarly, in the psychiatric patients, the active aggressive type was the one who usually excreted more noradrenaline.

Dr John I. Lacey (Yellow Springs, Ohio) said that in the individual the physiological indications of the imposed load were unevenly distributed. Each individual might react violently in one particular way, such as change in skin blood-flow or systolic blood-pressure, and Dr Lacey pictured a continuum between the random response at one extreme and the stereotyped response at the other.

DISTURBED BEHAVIOUR IN CHILDREN

Describing research on encopresis in outpatients at the children's department of the Maudsley Hospital, Dr E. J. Anthony (London) referred to three types of toilet training (coercive, normal cooperative, and neglectful) and to three main types of soiling disturbance—continuous (from infancy), retentive (with overflow), and discontinuous (after a period of bowel continence). In the group of children studied 75% of retentive encopresis and 63% of discontinuous encopresis was associated with a coercive form of training. On the other hand in 68% of continuous encopresis the training was neglectful. 80% of neglectfully trained children showed a weak 'aversion' reaction, as judged by a perceptual battery, was a need for the better integration of the concepts of the various facets of man, his physiology, the way he perceives and learns, his mental energy Some recent developments already made for better integration The electroencephalograph might provide a physiological measure of some aspects of personality and personal integration, and had suggested to Dr Grey Walter a physiological theory of learning

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[1] Selye H. *Lancet*, 1958, i, 1351

A recurring idea was that of matching with a pattern The raw material of experience was not the whole of the "blooming, buzzing confusion" which surrounded us but a selection of the regularities which we could detect, and these in turn provided the categories for the classification of further experience Conditioning depended on recognising regular relations between recurrent events in such categories Judgments of value were linked to situations recognised by their correspondence to some pattern previously experienced Expectation, then, played a large part in the organisation and disorganisation of personality, for what we knew consciously as expectation was only the exposed part of an iceberg that floated very low in the water

Conflict was not necessarily noxious in itself its outcome depended on the organisation of a given individual and his vulnerability to a particular form of stress Today the world was full of energy waiting to be borrowed, and the weakest signal might release gigantic force, for "the development of our mental powers has endowed us with so alarming a capacity for organisation —and disorganisation"

"PSYCHOSOMATIC?"

Prof Harold G Wolff (New York) distinguished between direct-acting stimuli (strong physical assaults, such as heat and cold) and those of lower intensity with an indirect action and the capacity to act as signals to the organism This division of stimuli corresponded closely to Professor Selye's non-conditional and conditional stresses Professor Wolff described an investigation into the medical history of 3500 people living in the United States, including 1700 semi-skilled women, 1500 skilled men, and smaller groups of Chinese graduates, Hungarian refugees, and recent American graduates preparing to be executives Of all the recorded illnesses in these 3500 people, two-thirds were concentrated in a quarter of the group Clusters of illness could be identified in many individuals, and the great majority of clusters occurred at times when the individual perceived his life situation to be unsatisfying or over-demanding, at times of threat to security or failure to satisfy important personal needs Statistical analysis supported the conclusion that illness-episode rate was greater at times of unsatisfactory life situation Professor Wolff's findings had made him uneasy about the validity of labelling certain illnesses "psychosomatic" There was no difference, it seemed, between peptic ulcer, gout, or breast cancer in their relationship to the patient's stress The majority of symptomatic illness (medical, surgical, or psychiatric) arose in, or might be remarkably influenced by, environmental circumstances which the individual conceived as threatening It might be that the life of the highly stressed person was telescoped in a way that brought him at an earlier age into the period of life at which malignant disease was commoner

DISORGANISATION OF BEHAVIOUR IN ANIMALS

Dr R A Hinde (Cambridge) discussed problems arising in animals beset by conflicting tendencies in natural or near-natural conditions In Nature higher animals were rarely single-minded the territorial song bird would attack conspecific animals which it encountered on its own territory, but it would flee from those it met outside that limit, encounters at the border of a bird's territory would evoke a confused response Conflicting tendencies might lead to the inhibition of all but one response or group of responses thus, a cat would not feed at a site where it had experienced alarm, even though it was starving The distinction between redirection activity and displacement activity in animals is very relevant in the attempt to relate animal to human behaviour In redirection activity an appropriate response may be directed to an inappropriate object both sexual and aggressive behaviour may be evoked by its mate in the male black-headed gull, and the mate may redirect the aggression to some passer-by In displacement activity, the action of the animal is apparently inappropriate starlings may suddenly preen their feathers during a fight, or they may show vigorous foraging movements before copulation Such displacement activity had been attributed to an "excess of drive", to "sparking over" from one centre of activity to another, but Dr Hinde was dissatisfied with this hypothesis The present trend was to look for common causal factors within the normal context In the deprived animal some link necessary for the chain of normal behaviour was missing, and the animal might respond to a stimulus that was usually inadequate Such a response might in fact be usefully adaptive, but it could result in bizarre stereotyped behaviour Two chaffinches deprived of material for nest-making plucked their breasts bare to feather their own nest In later nesting seasons, they continued to strip themselves of feathers, even though there was abundant nesting material available

Prof Martin Roth (Newcastle upon Tyne) reflected on the possible selective advantages of inappropriate displacement activity or repetitive activity Was the unresponsiveness of schizophrenics exposed to hard conditions in any way the outcome of a selective process?

Prof Howard S Liddell (New York) has for many years been investigating, at the Behaviour Farm Laboratory of Cornell University, the establishment of conditioned reflexes in animals and the generation thereby of experimental neurosis An observation which attracted much interest was that concerning differences in mortality between goats conditioned ("trained") during a period of separation from their mother and those trained while the normal relationship with the mother continued Of 10 young goats trained for a very short time (four to fourteen hours) without their mother, 2 died quickly, and hæmorrhages were found in the adrenal cortex at necropsy 4 out of 5 twin pairs trained without their mother died in their first year of life, but only 1 out of 5 pairs trained with their mother died in that time In Professor Liddell's experience, separation of the kid from its mother five minutes after birth could disrupt the maternal relationship, which could never then be established normally even though the period of separation was only a few hours Professor Liddell believed that all conditioning was neurotogenic—a view that was questioned by some members of the conference Prof G R Hargreaves (Leeds) remarked that all Professor Liddell's animals were much constrained passive recipients of noxious stimulants It might not be the conditioning that produced the neurosis Dr J chemical was not available. The mortality was reduced from 24.5% to 7.5%, and the duration of fever and of stay in hospital by about half. Haemorrhage and perforation remain serious complications, and in the gravely ill fluid and electrolyte balance is important. Dr. Vaizey reported the emergence of chloramphenicol-resistant strains of *Salmonella typhi*.

Duodenal Ulcer

Dr. A. A. Khan reported that in Africans in Kenya duodenal ulcer is on the increase. It affects all income, social and educational groups. It is a disease of young and middle-aged Africans, aged 18-45—the age-group that is likely to suffer the greatest conflicts, fears, and frustrations. As more Africans become urbanized, the incidence of duodenal ulcer may be expected to increase correspondingly.

Pulmonary Amoebiasis

Dr. L. B. Nevill drew attention to amoebiasis in its more severe and virulent forms in Nakuru and district. Of seven cases of pulmonary amoebiasis, in five the lung was infected via the liver and in two the infection was blood-borne. In all cases treatment with emetine and chloroquine was successful.

A Malabsorption Syndrome

Dr. A. G. Shaper said that steatorrhoea is excessively rare in Africans. He described one case, and referred to a second under investigation.

A 21-year-old Muganda presented with the "adult kwashiorkor" picture and investigation confirmed the presence of steatorrhoea and diffuse pancreatic calcification. At necropsy he was found to have pancreatic lithiasis, a fatty liver, and secondary atrophic changes in the small bowel, testes, and adrenals.

Pancreatitis was judged to play no part in the aetiology of this syndrome. Dr. Shaper holds that diffuse pancreatic lithiasis is distinct from the parenchymal calcification of chronic pancreatitis. The term "adult kwashiorkor" almost certainly embraces conditions of widely different aetiology and should be used with caution, if at all.

Drug Allergy and Contact Dermatitis

Dr. A. Henderson-Begg drew attention to the importance of history-taking in this type of case: patients who state categorically that they are taking no drugs or medicines may be found on specific questioning to be taking any of a wide variety of proprietary preparations, many of which (such as tonics, douches, contraceptives, and local anaesthetics) may not be regarded as medicines. In view of the large number of children today receiving sensitizing drugs, the incidence of drug allergy may be far higher in the rising generation. Dr. Henderson-Begg described four cases—two of aspirin allergy, one of phenolphthalein allergy, and one of contact dermatitis of the forearms due to paraphenylenediamine sensitization, with cross-sensitization to procaine.

Occasional Survey

KANAMYCIN

MAXWELL FINLAND
M.D.

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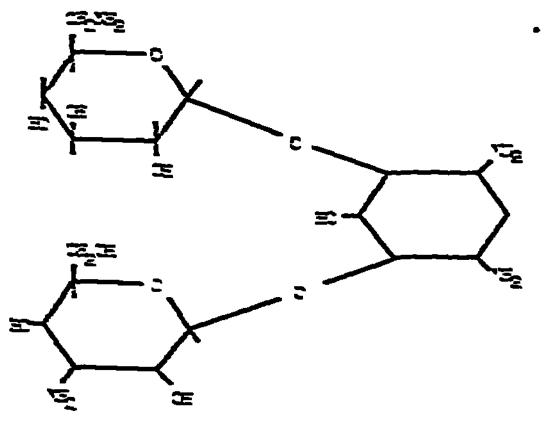
The increasing difficulties that are being encountered in the management of resistant staphylococcal and urinary tract infections and in the retreatment of cases of tuberculosis have stimulated interest in the development of new antibiotics that might prove effective in the treatment of such cases. Kanamycin, an antibiotic related to neomycin but exhibiting considerably less toxicity, is active against most of the causative organisms in such cases and should, therefore, be of interest. A conference on the basic and clinical research of this new antibiotic was held at the New York Academy of Sciences on July 10 and 11, and this paper represents a summary of the data presented at that conference.

The conference was concerned with the soluble, basic antibiotic, kanamycin, discovered by Umezawa and his co-workers in the fermentation products of *Streptomyces kanamyceticus*. Chemically this antibiotic was shown to be closely related in its structure to neomycin and to have some features in common with streptomycin but to be clearly distinct from both; it consists of 2 amino sugars linked glycosidically to 2-deoxystreptamine. The chemical structure and physical properties of kanamycin have been almost fully elucidated and, as the sulphate, it is remarkably stable, readily soluble, and suitable for intramuscular use.



The structural formula (see figure) was presented by Cron as the one that best fits all the known data.

EXPERIMENTAL EVIDENCE

In vitro, kanamycin was shown to be highly or moderately active against many common pathogenic aerobic gram-positive and gram-negative bacteria and mycobacteria; but some pneumococci, most streptococci, and pseudomonas were found to be moderately or highly resistant, and anaerobic organisms, yeasts, and fungi were nearly all highly resistant. Of immediate interest is its activity against pathogenic staphylococci irrespective of their resistance to other antibiotics now in common use. Its activity parallels very closely that of neomycin and of paromomycin. Resistance to kanamycin can be readily induced in staphylococci and in *Escherichia coli*, and this is accompanied by complete cross-resistance to neomycin and paromomycin and partial cross-resistance to streptomycin and certain other related antibiotics, but no cross-resistance with any of the other antibiotics that are generally available. Fresh isolates of various bacteria also show this cross-resistance among kanamycin, neomycin, and paromomycin, but streptomycin-resistant strains do not show cross-resistance to kanamycin and to the other related antibiotics. In the tubercle bacillus there appears to be complete cross-resistance between kanamycin and neomycin and one-way cross-resistance from viomycin to kanamycin.

In the usual laboratory animals kanamycin has shown relatively low acute toxicity. Subacute and chronic administration revealed toxicity that was similar to, but slightly less than, that of streptomycin and dihydrostreptomycin and much less than that of neomycin. In particular, the adverse vestibular and auditory effects occur in experimental animals after larger doses and after but 76% of those coercively trained reacted strongly A group of children with sleep disturbances were compared with neurotic controls to assess the influence of various factors suggested as causes of sleep disturbance Significant differences were found which pointed to sleeping in the parental bedroom, separation trauma, and phobia in the mother as important influences

PSYCHOSOCIAL REMEDIES

In the discussion on the prevention and treatment by psychosocial means of psychiatric reactions to stress, Dr J D **SUTHERLAND** (London) expressed doubts about present-day psychiatric institutions Too many, he felt, still isolated and repressed the patient. They must become open systems having much more communication with society Dr Sutherland's colleague at the Tavistock Clinic, Mr Eric Trist, had been investigating the sociotechnical system, the complex matching of social and technical factors in the individual's working environment If the matching was inadequate, tension resulted, and a thorough analysis of the circumstances could often indicate the right remedy

APPRAISALS

Dr **DENIS HILL** (London), in a skilful review of the first three days of the conference, drew together some of the threads He recalled how rarely the word "stress" had been used until comparatively recent years Freud had not used it, Darwin was the one who came nearest to it in his definition of the struggle for existence He did not think that the stressor could be defined it owed its stressing quality to the nature of the individual, and it was the meaning of experience that mattered This importance of the meaning of a stimulus to the organism stimulated recurred throughout the discussions Dr Hill had found Dr Hinde's views on animal behaviour to be in line with clinical experience He pointed specially to Dr Hoagland's finding that the better the individual's performance at a task the less his steroid output and, in one sense, the less the stress he sustained; and to Professor Selye's demonstration that the duration of stress determined its effects Dr Hill attached importance also to Dr Lacey's view that the autonomic nervous system was *not just an atavistic instrument, not just an efferent* system, but one which had important feedback functions The conference, he thought, should direct its attention not to effects but to the stress process itself And in that inquiry Dr Hinde's guidance on the features of displacement behaviour in birds might be relevant to the study of tics and compulsions in man

Action in some form relieved tension man sought to escape from the prison of his social environment Any prolongation of stress, any delay in the adaptive process was damaging to mental and physical health, and could even, it seemed, shorten life It could also be argued that a neurosis was therefore preferable to continued stress

Prof R W **GERARD** (Ann Arbor) proposed a transliteration from the psychosocial to the neurophysiological He pictured the build-up in the nervous system of stimuli generated by maintained uncertainty, leading to reverberation and the continued passage of messages round looped systems If such stimuli went round long enough they became permanent Such a process could contribute to learning Hamsters who had found their way through a maze would remember and benefit from their experience only if they were given time to do so If their brains were stunned electrically immediately after the animals had explored the maze, they did not remember When the reverberating disturbance was sufficiently great the stimulus could spread to the hypothalamus An increasing number of cells became involved and finally the whole neurone assembly was committed, so that no cell reserves remained At this stage, in Dr Gerard's hypothesis, non-adaptive stereotyped behaviour predominated

ASSOCIATION OF PHYSICIANS OF EAST AFRICA

THE annual conference was held in Nairobi, under the presidency of Dr A D **CHARTERS**, on June 26-28

Tuberculous Pericarditis

Dr P P **TURNER** said that tuberculous pericarditis is common in East Africa and is commonly fatal There is no specific physical sign, other than a friction rub Culture of fluid from the pericardial sac is positive in about a third of the cases. Removal of fluid is often essential in cardiac tamponade and produces dramatic improvement Dr Turner recommends treatment with antituberculous drugs, prednisone, and intrapericardial hydrocortisone

Ménière's Disease

Mr J F **JARVIS** described recent work on the microchemistry of the labyrinthine fluids and the finding of a high potassium content in the endolymph The electronystagmograph promises to widen understanding of nystagmus as a sign of labyrinthine disease

Treatment is still largely empirical and aims at removal of the cause, palliation of symptoms, and destruction of a useless and disturbing labyrinth

Allergic Dermatosis

Colonel H **WILLIAMSON** said that in treatment of allergic dermatosis the cortisone group of drugs is outstanding, these are harmless if given judiciously Possibly, disturbed cortisone secretion may explain the well-known association between emotional stress and allergic dermatosis

Histoplasmosis in East Africa

Dr P E C **MANSON-BAHR** said that *histoplasmosis* has been shown to occur in East Africa in the localised, disseminated, and benign pulmonary forms *Histoplasma capsulatum* lives in the soil in its mould phase and invades the body from dust. In Africa a large form—*H duboisii*—has been described. In the U S.A histoplasmosis is not uncommon, as is evident from small epidemics of the benign pulmonary form, a high prevalence of skin sensitivity, and a high prevalence of pulmonary calcification with positive skin histoplasmin tests *In* Africa all forms of the disease have been described, in East Africa Dockeray (1957) has described a localised granuloma of the pharynx, while Davies (1957) has described a fatal case of disseminated disease in a 2½-year-old European child

Dr Manson-Bahr described a case of benign pulmonary histoplasmosis or "cave disease" in a European male who had visited the Amboni caves near Tanga in Tanganyika, where the floor was covered in bat guano Fourteen days after exposure he became febrile with rigors and sweating There were no physical signs, but he had a persistent brassy non-productive cough *Radiographs* showed numerous coarse miliary granulomas throughout the lungs, which persisted for six months A histoplasmin skin test was positive No treatment was of any avail, but the patient gradually recovered

Stott (1954) found that of African adults in Kenya 8 5% reacted to histoplasmin, and of a group of miners from the Nyanza province 14 6% reacted Histoplasmin surveys can be expected to reveal further evidence of this disease in East Africa

Typhoid Fever at Mulago

Dr J M **VAIZEY** compared the cases of typhoid fever in Mulago Hospital in 1957, when chloramphenicol was available, with the cases in 1949, reported by Musoke[1], when chloramother more effective and less toxic agents are available Its major toxic effects on the kidney and eighth cranial nerve can probably be minimised to a certain extent by some caution in its use

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[1] Musoke, L. K. *E. Afr Med J* 1952, 29, 209

The similarities and differences in the known chemical structure of kanamycin, neomycin, and the streptomycins and in the renal and eighth-nerve toxicity which they produce offer an opportunity to explore the specific relationships between the structure of these antibiotics and the toxic effects they produce This may lead to a better understanding of the basis of their production and possibly to means of preventing or alleviating them

Medicine and the Law

"False" Certificates

A DOCTOR was charged at Glasgow Sheriff Court under the National Insurance Act 1946 with making false statements on medical certificates [1]

The patient had had an operation on his right foot in June, 1957 While being treated as an outpatient he regularly called on his doctor for medical certificates, but on Dec. 7 he was sent to prison for 30 days for housebreaking

The patient's wife then twice called on the doctor and asked for her husband's certificates, explaining that he was in bed because his foot was swollen On the second occasion the doctor told her that he ought to see the patient before issuing the certificate. She confessed in court that she had lied because she was ashamed to admit that her husband was in prison.

It was submitted in defence that it would be outrageous to convict the doctor, who had done nothing wrong as the certificate was substantially accurate He was acquitted

Prison Sentence for Attempted Suicide

AT Cheltenham magistrates' court on July 17, an unemployed man of 59 was sentenced to six months' imprisonment for attempted suicide [2]

On June 8 the police had visited the man's house and found his wife dead in bed and the man sitting in a chair with a bullet embedded in his head He first appeared before the magistrates on June 26 when he pleaded guilty to attempted suicide and the possession of a revolver without a firearms certificate He was remanded for three weeks to Gloucester prison for a medical report

When he appeared before the magistrates again last week a police chief inspector said that the man had previous convictions for fraudulently drawing unemployment benefit, using threats, running away and leaving his children, assaulting the police, and committing an act of indecency The man admitted the convictions, but said that they were due to domestic trouble

The clerk to the magistrates said that the prison doctor's report recommended that the man should receive medical treatment, which could only be given at Coney Hill Mental Hospital, and that he should be put on probation for three years subject to his becoming a compulsory inpatient at that hospital The man was willing to comply with this condition

In sentencing him, the presiding magistrate said

"We think you could have done a lot better for yourself, you know You have not made all that effort to go straight or live honourably We have taken into account what has happened to you domestically and also we have considered your character We think the proper thing to do in your case is to send you to prison where you will receive the medical treatment you need"

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[1] *Scotsman*, July 15, 1958

[2] *Gloucestershire Echo*, July 17, 1958

In England Now

A Running Commentary by Peripatetic Correspondents

SEEN at 7 A M, the Wooloomooloo Private Hotel seemed to need a fire-brigade rather than a doctor The front hall was solid with blue smoke, through which Mr Robinson's Australian accent informed me that it was a fair cow as the kippers had exploded and set the curtains on fire while he and his wife were giving first-aid to the new lodger

"Cut her head on the wash-basin, doin' her early-morning reducing exercises I only wish I had some of her weight," said Mrs Robinson, whose two most prominent anatomical features were ears "Blood all over the new wallpaper, too—I told Fred we should have chosen the red geranium pattern Now we shall have to move the wardrobe in front" I interrupted Mr Robinson's disapproval of this idea by suggesting we went above cloud and saw the patient, but was told that there was no hurry as she was drinking tea and asking what there was for breakfast. I wondered whether the blow had damaged her olfactory nerves

Led by Mr Robinson, who resembled the Spectre of the Brocken, we stumbled upstairs in a hot vertical draught of kipper-smoke, to which each landing added contributions of onions, toast, coal-gas, and cabbage Permeating the whole, like harp music through a full orchestra, came suggestions of cat Charred fabrics, soot, and carbon copies of kippers fluttered about us, and shadows of inquisitive lodgers fled fearfully back into the reek at Mr Robinson's roars of reassurance These disembodied bellowings from the clouds produced a curiously Old Testament effect, heightened by a sudden thunderous hammering Mrs Robinson halted and clutched the bannister

"Nay dammit! That's Grandad stuck in't W again Ah told 'im not to go without 'is teeth in" I tried hopelessly to see the connection

"T'lock sticks if you lock it, so you've to whistle to keep folks out and Grandad can't whistle without 'is teeth so now t'lock's stuck"

"Just wouldn't it!" snorted Mr Robinson reappearing in red-eyed fury "An' all because that girl has to do slimming exercises to an (Australian) gramophone From the noise she makes every morning I reckon she puts the record on the floor, holds the needle on it with one hand, an' gallops round and round it"

"Nay, I blame her young man," said his wife, loyal to her sex. "I've asked her, but she just gives me a right sad, enemetic smile like that there portrait of who-is-it "

"The Mona Lisa?" I suggested

"Too —— right, Doc!" said Mr Robinson enthusiastically "She's the biggest moaner in the house"

"Listen who's talking!" retorted Mrs Robinson, adding accusingly "Ah'll bet that tea you gave 'er 'ad sugar in it"

"O' course it —— well did I was treating her for shock"

"She's reducing Sugar's bad for it."

"Well aren't you a silly woman, you silly woman," shouted Mr Robinson, shaking the bannisters "First things come first!"

"Like I say—she was fat before she was shocked "

I left them to it and entered the patient's room, where I put a dressing on a fat and dishevelled girl's scalp After thanking me, she said, "I don't know why I get so dizzy doing these exercises"

"I do," I said, looking at the gramophone "You're playing a 45 r p m record at 78"

* * *

We medicals sometimes cock a snook at our legal colleagues steeped in precedent and advancing, as we think, from before backwards But in the matter of space travel and moon habitation they are ahead of us As one of my peripatetic colleagues pointed out last week the psychiatric implications of the subject are still largely unexplored, yet the American Bar already has a committee on the law of outer space They cannot, however, shake off the earthy past altogether and quote the longer periods of administration than with streptomycin and dihydrostreptomycin, respectively, and the renal toxicity of kanamycin is much less marked than that of neomycin and requires much larger doses given over longer periods

Absorption and excretion from subcutaneous and intramuscular doses in animals and from intramuscular doses in human beings is rapid Peak concentrations from intramuscular doses are usually achieved in the serum in about 1 hour and these vary with, but do not exactly parallel, the size of the dose Exact dosage regimens cannot yet be established, but the rapid fall in blood levels indicates that intramuscular doses must be given at 6-hourly intervals in order to maintain adequate therapeutic levels, except for doses of 1 0 g which may be given at 8-hour or even 12-hour intervals Excretion of kanamycin is primarily into the urine and it is cleared by glomerular filtration only About one-half to as much as four-fifths or more of the intramuscularly administered dose is accounted for in the urine within 24 hours Oral doses are very poorly absorbed, and doses of 3–6 g daily appear to be effective in altering the bowel flora There appears to be no excessive binding of kanamycin to serum-protein and no evidence of cumulation Average peak concentrations in serum from doses of 0 5–1 0 g in adults are such as to permit inhibition of the more sensitive organisms, including staphylococci and mycobacteria, and of many susceptible but less sensitive ones (salmonella, shigella, and many strains of proteus), particularly with large doses

CLINICAL APPLICATION

Clinical results reported here from the intramuscular use of kanamycin were highly satisfactory in a large proportion of cases of staphylococcal infections, including many severe cases in which the organisms were resistant to other antibiotics, particularly penicillin, streptomycin, and the tetracyclines It appears to be highly effective in acute gonorrhœa in males and it was effective in most cases of severe anthrax infections The antibiotic has also proved effective in many acute and chronic infections of the urinary tract that resisted treatment with other antibiotics, but chronic infections with pseudomonas, enterococci, and some proteus strains appear to be resistant, and failures were reported in infections with such strains and in pneumococcal and streptococcal infections

Kanamycin given orally in doses of 4–8 g daily was found to be an effective inhibitor of aerobic intestinal bacteria comparable to neomycin and useful in the preoperative preparation for surgery of the large bowel It has been effective in the prevention and treatment of hepatic coma in a few patients with advanced cirrhosis of the liver in whom it has been tried and in reducing the level of ammonia in the blood of such patients, it apparently can be used together with chlorothiazide in such cases Favourable results were also reported from intramuscular or oral therapy in some salmonella and shigella infections, but not uniformly so in severe salmonella infections or typhoid Intraperitoneal instillation has been used successfully in established peritonitis and for peritoneal contaminations, but the possibility was raised that in some cases it may be followed by adverse respiratory effects when used in conjunction with ether or curare, although such a synergistic effect was not evidenced in dogs even with large doses of kanamycin

In the treatment of tuberculosis, the limited experience of American clinicians employing kanamycin alone in severe chronic and resistant cases suggests only that it exerts some favourable effects on the disease, but this was not very striking and resistance to kanamycin was rapidly acquired by the organisms Japanese experience with kanamycin given together with adequate daily doses of *p*-aminosalicylic acid (P A S) in more favourable cases, and as initial treatment, indicates that the two agents together exert clinical and bacteriological effects that are approximately comparable with streptomycin and P.A.S. used in the same manner It appears to be effective against infections with organisms that are resistant to streptomycin, isoniazid, or P A S' Kanamycin-resistant organisms that emerge during treatment are also resistant to neomycin, but streptomycin-resistance is not acquired in the process

TOXIC EFFECTS

Toxic effects observed thus far have generally been mild or moderate, serious toxicity has been encountered only rarely Local irritation from intramuscular injections has been slight and has rarely interfered with continued therapy Sensitisation, drug fever, and drug rashes appear to be infrequent, but eosinophilia appears to be frequent in patients treated for a week or longer

The major toxic effects are on the kidney and eighth cranial nerve Hyaline and granular casts are seen commonly in the urine, they may appear early, usually persist throughout treatment, and generally clear soon time after the treatment is stopped This is sometimes accompanied by the appearance or increase in leucocytes and occasionally by small amounts of albumin in the urine, but only rarely by elevation of blood-non-protein-nitrogen or by oliguria The evidence indicates that renal functional impairment, usually mild, occurs in more than a quarter of the patients, involves both glomerular and tubular function, and probably is wholly or largely reversible Reports on kanamycin treatment of patients with initially impaired renal function are too few to judge the effects in such cases, but such treatment should be undertaken with caution, where the underlying renal impairment is related to pyelonephritis, it may actually improve if the treatment favourably influences the infection

Vestibular damage appears to be infrequent, but loss of hearing, beginning in the high-frequency range, appears to be quite frequent on subacute or chronic administration of effective doses, especially with large doses and prolonged treatment Tinnitus is an early and important warning sign of eighth-nerve damage Audiometric tests should be done frequently during continuous administration, especially in patients with impaired renal function, or during prolonged treatment, or when large doses are used There is some evidence that the deafness may not always be bilateral, symmetrical, or permanent, it always appears and reaches its height during treatment Delayed appearance of deafness after stopping treatment was not noted, but the possibility of cumulative toxicity on retreatment must be considered

Unlike parenteral therapy, oral administration of kanamycin is usually well tolerated even in large doses and produces no toxicity except for occasional diarrhœa

CONCLUSION

Kanamycin thus appears to be a useful antibiotic for the treatment of certain troublesome bacterial infections It should not be used in the treatment of pneumococcal, streptococcal, brucella, or other infections in which the results have not been altogether favourable and for which

HAZARDS OF CHLOROTHIAZIDE THERAPY

SIR,—Chlorothiazide (' Saluric ') is now being extensively prescribed in general practice, for there can be little doubt as to its efficacy as a diuretic Certain precautions are, however, required in its use and our experience in a large hypertensive clinic suggests that prescribers are not always aware of the potential dangers of the new drug

Chlorothiazide under some circumstances causes a considerable diuresis of potassium in addition to that of sodium If the potassium is not replaced this can rapidly lead to hypokalæmia and symptoms of muscular weakness Hypokalæmia also potentiates the effect of digitalis derivatives and signs of digitalis overdosage may occur in digitalised patients given chlorothiazide Ideally, the plasma-potassium concentration should be followed serially during treatment, but in practice the administration of 3 g of potassium chloride on the days when chlorothiazide is given would appear to obviate the risk of the development of hypokalæmia If, however, renal failure is present potassium chloride should not be given unless the plasma-potassium concentration can be followed at short intervals

Chlorothiazide also potentiates the action of the hypotensive drugs mecamylamine and hexamethonium, and an excessive fall of blood-pressure may occur if chlorothiazide is given to a patient whose blood-pressure is already adequately controlled by ganglion-blocking drugs

We feel that these hazards of chlorothiazide therapy are not sufficiently widely appreciated

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M L ROSENHEIM
E J ROSS

N.H.S. STAFF COLLEGE

SIR,—As Dr Fielding (July 12) referred to the Administrative Staff College of King Edward's Hospital Fund for London, a reply from me may not be out of place This staff college, of which I am chairman and which opened in 1951, has been endeavouring to do just what Dr Fielding advocates—to create " a working partnership between medical, nursing, and lay personnel to define each partner's proper sphere of activity, and to infuse that sense of common purpose which the service so badly needs "

The college has never aimed at providing refreshment solely for " lay " administrators Doctors have attended many of the courses planned for senior administrative officers, and courses have been held for physician-superintendents of mental hospitals, for finance officers, and even for hospital chaplains Meetings are arranged with the nurses attending the Fund's colleges for ward sisters and for matrons The possibility of offering a " mixed " course—doctors (and not just hospital doctors), nurses, and " lay " administrators—has been discussed, and even a short conference of chairmen of hospital management committees is in contemplation

The courses are all residential and discussion is the rule rather than formal lectures Many hundreds of administrative officers have passed through these staff colleges, and there is reason to believe that most, if not all, have benefited from the experience The colleges are not large—a discussion group of about a dozen seems best—so the numbers dealt with at any one time have to be restricted, nor can the Fund cater for the whole of the country Our ideas as to the future of the staff college are by no means fixed, so the Principal will welcome inquiries from interested doctors His address is Hospital Administrative Staff College, 2, Palace Court, London, W 2

King Edward's Hospital Fund for London,
34, King Street, E.C.2

WILSON JAMESON

RADIATION HAZARD IN ANTENATAL RADIOGRAPHY

SIR,—Dr Dempster (July 19) is to be congratulated on undertaking a prospective study of radiation hazards in antenatal radiography it is to be hoped that others will follow his example, thus accumulating the really large body of data which is necessary for study by this method In the meantime we would like to point out that a negative result obtained from a ten-year follow-up of 116 live-born infants in no way conflicts with the findings of our own survey, recently published in full[1]

The proportion of infants born in 1948 who died of malignant disease before reaching their tenth birthday is probably below 0 8 per 1000 If a typical pelvimetry examination doubles this risk, the odds against finding even 1 case in a sample of 116 would be nearly 5 to 1

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ALICE STEWART
J W WEBB
D HEWITT

BONE-MARROW TRANSPLANTATION IN BLOOD DISEASES

SIR,—Your leading article last week refers to the immunological obstacles encountered in this form of treatment To a certain extent the position has been clarified since the Boston conference and there now appear to be two separate problems

Rejection of the graft by the host occurs when enough immunologically competent cells remain after the onslaught of both disease and treatment The problem here is to discover an agent capable of destroying all the neoplastic cells as well as the native immune-reactive cells, and although this may seem a distant prospect there is, perhaps, one source of hope Hitherto, the effect of any form of therapy has depended on exploiting a difference between neoplastic and normal tissues of the same sort—i e , leukæmic cells versus normal marrow or lymphoid cells—whereas now the difference is widened and lies between neoplastic cells and susceptible normal cells of other organs (e g , intestinal mucosa), since one can afford to destroy all normal hæmopoietic cells This is a biochemical challenge

In the long run, however, the graft-versus-host reaction may be of greater importance A rejected graft can, perhaps, be replaced, but a rejected host will die of secondary disease The solution here, as indicated by the work of Medawar and his colleagues, lies in the use of fœtal material which may by virtue of " adoptive tolerance " accept an antigenically different host Both Barnes et al[2] and Uphoff[3] have published experiments demonstrating survival with fœtal tissue in strain combinations where adult tissue regularly causes fatal secondary disease

That fœtal cells can be safely used in man was demonstrated in one case by Thomas et al ,[4] and we have similarly treated seven cases without fatality In one case at least there appears to be evidence of a " take " as judged clinically, by serial marrow biopsies, and by the presence of circulating foreign erythrocytes Details will be reported in due course.

Meanwhile two further points deserve attention Not all histocompatibility barriers in mice can be overcome

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[1] *Brit med J* 1958, i, 1495
[2] Barnes, D W H., Ilbery, P L T , Loutit, J F *Nature, Lond* 1958, 181, 488
[3] Uphoff, D E *J Nat Canc Inst Wash* 1958, 20 625
[4] Thomas, E D , Lochte, H L , Jr , Wan Ling Chu, Ferrebee, J W *New Engl J Med* 1958, 257, 491

Roman law of "ownership *ad coelum*" to mean extend upwards only to that point "where there is sufficient gaseous atmosphere to provide a measure of aerodynamic lift" beyond which is "*res extra commercium*" The moon, at present "*res Nullius*", is thus, we are told, capable of appropriation by effective occupation

Obviously, we should give more attention to health conditions in space and less to N H S conditions in this planet Couldn't the Royal Colleges, in the intervals between examinations, set up a committee on lunar nosology? Once we colonise the moon there are certain to be public-health problems—water-supply, sewage disposal, clean air, and so on—about which we could anticipate intelligently The first settlers, of course, should be our deaf mutes For them the soundless satellite will have no communication difficulties The second batch should be our bacteriologists to tend their cultures of cocci and viruses in an unfriendly land

I have always been a bit confused about the vagaries of lunar time and temperature, particularly on the blind side But they will provide interesting thesis pabulum for the next generation—the children who today smile at us Newtonians and are at home in this new cosmos of interchangeable matter and energy, elastic time, and curved space

* * *

The girl had wanted a certificate to be "off work" because of the "pressures in her head" She was the last patient and as I left the surgery feeling vaguely guilty, I wondered how I could justify that certificate

Curiously enough I found that same evening that the answer had been provided in 1560 by St Theresa To Nuns who "*have only a headache, but leave off going to the choir as* though that would kill them", she wrote

> "You may ask, why does the prioress give the dispensation? Perhaps if she knew your interior she would refuse, but as you inform her of your need and a doctor to whom you have said the same is not wanting to support you, and a friend or relative is weeping near, what can she do? She has a scruple lest she fail in charity, and she would rather you should be at fault than she"

How opposite to medicine But isn't there a sting in the tail of that quotation?

* * *

For most of us botany is a dim forgotten far-off thing of 1st M B long ago, and when our local medical society took an afternoon off from the discussion of typhoid and hookworm to visit the East African Forestry Research Organisation most of us learned for the first time of the ruthless racialism of the agricultural scientist In demonstration of plant diseases, a detailed clinical history with attention to sources of stress was perhaps hardly to be expected, but it was strange to find neither the patient nor the disease attracting much attention Instead the limelight was focused on the hero of the day—the resistant race Some judicious matchmaking followed, and by the third or fourth generation a paragon appeared—resistant yet fruitful to live happily ever after

Pondering on the possible application of such methods in human disease, I could picture the totalitarian countries forging ahead while the democracies rely on such half measures as a subsidised bride-price in cases approved by the Minister

* * *

Looking round at my colleagues the other day, all of them M—B, D, CH, S, R C S, or R C P, it struck me that there was room for yet another qualification There is one which I could, in all modesty and with a clear conscience, bestow on myself—M N (Nullorum Magister, or Master of None) Surely that would be an appropriate recognition for the hours of house-painting, plastering, wallpapering, gardening, cooking, baby-minding, washing up, carpet-laying, and car-tinkering which we all add to our more academic activities in these days of widening horizons and shrinking specialties

* * *

I hear that surgical caffeine-addicts are now trying to get their elevenses past the auditors by describing them as "opaque media" or "nutrient broth"

Letters to the Editor

THE PLACE OF THE RESEARCH INSTITUTE AND THE ADVANCE OF MEDICINE

SIR,—Although Sir Charles Harington's Linacre lecture[1] is most impressive in its range and understanding, I think there is one point of criticism of research institutes which he mentions briefly but does not answer—that research units withdraw the younger workers from university teaching

It is common ground that the research institutes require well-trained workers If the interests of university and research institutes conflict, Sir Charles suggests that those of the university should come first I do not think this is achieved by present policy

The most important part of the training of medical research-workers in this country is the course for an honours degree—for the Natural Science Tripos, Part II, at Cambridge, the Final Honours School at Oxford, the B Sc Special at London, and similar courses in the English provincial and some of the Scottish universities. For such a course it is essential to have at least half a dozen first-class university teachers to teach a variety of aspects of the subject These teachers must have sufficient research experience to have the respect of their pupils, some personal acquaintance with the borderland of knowledge, and the mental agility to meet a student in tutorial work on his own ground This last, alas, tends to disappear with increasing eminence and advancing years

It is extremely difficult to get such teachers and to keep them The attractions of research institutes include better laboratory equipment and facilities, more time for research, more technical assistance, freedom from correcting examination papers, and, in practice, better pay In addition, there is the prospect of becoming a head of a department by returning to the university in due course It is not surprising that an appreciable number of these men leave universities for research institutes

In return, the universities are offered men from research institutes whose sources of inspiration for research have dried up, and professors of eminence who have had no teaching experience at all, or none for the last ten to fifteen years While Oxford and Cambridge will no doubt continue to retain the tutors and supervisors they need, it is difficult for other universities to provide counter-attractions It seems that the supply of scientific man-power is limited, and that the share likely to reach the basic medical sciences is not likely to increase

I would therefore suggest to those responsible for long-term planning that research institutes should cease to recruit staff at or before PH D level, and that it should be exceptional to appoint anyone to established staff unless he had at least five years' teaching experience This would make the re-exportation to universities of both unsuccessful and the most successful research-workers rather easier As a longer-term measure, I suggest that, instead of building further isolated research institutes, every effort should be made to site research units within universities and that their staff should take part in the teaching of undergraduates at honours level There are difficulties in this proposal, but in some universities they have been successfully overcome

Department of Physiology,
University of Edinburgh

D WHITTERIDGE

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[1] *Lancet*, 1958, i, 1345

Wroblewski et al deal with alanine-ketoglutaric transaminase as a more sensitive index of hepatic damage We feel therefore that it is unjust to attribute to Wroblewski and his colleagues the discovery of the diagnostic value of the serum-transaminase activities in virus hepatitis

We should like to draw the attention of Dr O'Brien and his colleagues (June 14, p 1245) to a report[12] on both the transaminase activities and their ratio, on phosphoglucomutase activity, and on fumarase activity as indices of the effectiveness of prednisone therapy in virus hepatitis

FERNANDO DE RITIS
MARIO COLTORTI
GIUSEPPE GIUSTI

Institute of Medical Pathology,
University of Naples

NO MORE NEOLOGISMS?

SIR,—We must all sympathise with Mr Norman Lake's dilemma Nevertheless his conclusion, at least as reported in your columns (July 5, p 40), that the addition of the new word "hæmorheology" to medical jargon is justified must not go unchallenged. The term seems to have been invented by Dr A L. Copley, and again to quote your report of the meeting at Charing Cross Hospital, covers "the deformation and flow—i e, rheological—properties of cellular and plasmatic components of blood in macroscopic, microscopic and sub-microscopic dimensions and the rheological properties of vessel structure with which blood comes in direct contact"

The subject as defined by Dr Copley has been studied before, not entirely without success, by such men as Harvey, Malpighi, Lister, Krogh, and Florey, to name only a few As far as I can recall they did not find that in order to study what was happening to the blood-flow in relation to the vessel wall a new term was necessary Why then should it be needed now? Is it to clarify or to obscure? Unfortunately the latter is the only tenable conclusion

This issue is so trifling in itself that I would not have bothered to raise it were it not that this is no isolated instance It is merely a rather striking example of a growing tendency among medical and other scientific writers to obscure their own thoughts and to hide them from other people by clothing them in unnecessary jargon Thus, a paper by a very talented scientist and writer who is a personal friend of mine contains the following sentence "A rate of infusion of 15 mg per kg per hour (of chlorothiazide) *induced natriuresis, kaluresis, chloruresis and bicarbonate excretion*" Now the unfortunate scientist who is not a renal physiologist cannot find these words in a dictionary, unless he knows Greek he cannot be sure of their meaning, and even then it can only be a guess Why did not he write "increased the excretion of sodium, potassium, chloride, and bicarbonate" It would have been no less accurate, rather shorter, and easily understood by all The reason was clearly that he fell unthinkingly into one of the bad habits of the time As to why this bad habit has arisen at all is a question which perhaps you may allow me to discuss in your columns on another occasion

Now this is a very serious problem, the more serious perhaps because it is so little ventilated It is the ancient and honourable objective of men of science to discover scientific truth by observation and experiment and to make it known The introduction and use of unnecessary scientific jargon seems to me to be flatly opposed to this objective Is it too much to hope, Sir, that your journal, which has so often given a courageous lead in the past, should declare that in the future it intends to uphold the dignity and purity of the English language and not to allow the use of technical neologisms unless they are clearly defined and an unanswerable case made out for their use

Oxford GEORGE PICKERING

SIR,—Reading in *The Lancet* during 1957 only those articles likely to interest a general physician, I came across the following words, which appear neither in the *Concise Oxford Dictionary* nor in the latest (1957) edition *Stedman's Medical Dictionary*

Allergology
centrencephalic
oxalosis
chylomicra
ephebiatrics
ataractics
algometer
hypohyperparathyroidism
polypectomy
pathophysiology
cholangiolitis
neurosophical
dysraphicus
undervascularised
cardiomyopathy
rhabdomyolysis
transfusionists
centrizonal
thoracologist
histogram
ataralgesia
pulhestibs

In addition, the following words, though listed in Stedman, would be difficult to justify

Cholestasis
antigenicity
hyposthenuria
angiolymphitis
defibrillation
anæsthetologist
uricosuric
normovolæmic
phlebarteriectasis
angiology

Stedman's Dictionary now contains 1656 large pages Since the 1953 edition, over 4000 new words have been added—nearly 3 new words a day When is this verbal flood going to abate? You, Sir, have added to the deluge, but I plead with you not to allow any further new words to appear in *The Lancet* unless a very good case can be made out for them

Some new words are merely ugly cacophonous polysyllabic accretions, more appropriate to German than to English Many other new words have been perpetrated because the writer has been leaning over backwards to avoid the suffix "itis" It is true that "itis" in Greek signifies inflammation, but by "inflammation" the Greeks referred to any lesion which produced either swelling or redness or heat—any one and not necessarily all three Examiners, it seems to me, are especially prone to ill-justified quibbling over the suffix "itis", and a well-known textbook, after insisting that the term "retrobulbar neuritis" be reserved for inflammatory lesions, mentions that "an optic neuritis is secondary to a retinopathy" The time is ripe for an agreement that "itis" implies "a lesion of", not necessarily an inflammation Otherwise future journals will add still more needless new words to spondylosis, neuropathy, retinopathy, cheilosis, myelopathy, &c

Some writers have replaced the prefix "a" (or "an") meaning "without" by "hypo", which implies a diminution rather than a complete absence, thus hypoxia, hypalgesia, &c But we all realise that complete absence of anything is rare in clinical medicine

Surely language is determined largely by common usage, and new words should not be invented purely on etymological grounds—which are often inaccurate

London, W 1 M H PAPPWORTH

*** Were we to insist, as Sir George Pickering suggests, on an "unanswerable" case before admitting a technical neologism to our columns, we should be putting what seems to us an unreasonable constraint on contributors, and if we adopted Dr Pappworth's relentless standards, we had better put on our contents page "no neologisms allowed" Rightly or wrongly, we judge the ones that come before us less strictly than either of our correspondents, in the belief that the construction of a new word is sometimes a praiseworthy, though not always successful, attempt to improve communication Some of the words by using fœtal tissue (Uphoff, personal communication) What then are the equivalent distinctions in man? Are they perhaps identical to the major blood-group antigens? Secondly, is it desirable to include with the marrow transplant as much lymphoid tissue as possible, in particular splenic cells, with a view to providing the means of resistance to the infections which inevitably occur in these patients? If secondary disease can with certainty be avoided the answer is yes, but it yet remains to be seen how soon fœtal cells transferred to an adult environment become capable of immune reactivity

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[12] De Ritis F, Coltorti M Giusti, G Atti del 57 Congresso della Società Italiana di Medicina Interna, p 114 *Clin chim acta* (in the press)

Royal Marsden Hospital,
London, S W 3

M CONSTANDOULAKIS
H E M KAY

WORLD HEALTH ORGANISATION

SIR,—In his review (July 12) of the first decade of the World Health Organisation, Dr H S Gear restates the principles on which the Organisation was conceived, and examines how far they have been applied One of these principles is that membership should be universal, and Dr Gear refers to 88 States which belong Undoubtedly the most serious defect is that China is "represented" by the Government in Formosa The loss is not only China's, since it is clearly undesirable epidemiologically that a vast land mass and 650 million people should not contribute to, as well as share in, international health coverage At Geneva recently a senior W H O official gave me an example from the recent influenza pandemic The virus was first isolated in China, and had that country been a member of W H O the strain, as well as early epidemiological information on the epidemic, would have been automatically made available to the Organisation As it was, it appears that three valuable months were lost before the virus was isolated elsewhere

London, N W 3

P D'ARCY HART

WORKING PARTY ON HOSPITAL MEDICAL STAFFING

SIR,—The consultants and specialists of the regional-board hospitals note with concern that the working party to inquire into the staffing of hospitals does not contain a direct representative of the provincial non-undergraduate-teaching-hospital staffs Most of the hospital work in the country is done in regional hospitals, whose staff comprise the greater proportion of the nation's specialists Most of the problems involved in staffing at consultant and registrar level concern these hospitals It is our earnest hope that every endeavour will be made to take evidence from the staffs of such hospitals in order that the problems involved may be effectively solved

It is possible that the extent of staffing difficulties and the pressing conditions which have led to the present situation have never been fully realised, because those at the helm on various consultant committees have been trained and work mainly in teaching hospitals where the conditions of service are different and more leisurely The turnover of patients, both emergency and routine, is higher in the regional-board hospitals Members of non-teaching hospitals have contributed generously to the success of the regional hospital service, but the "slack" in their establishments was taken up years ago and new consultant and registrar establishments are overdue

London, W 1

HAROLD DODD
President Regional Hospitals Consultant and Specialist Association

CRASH-HELMETS

SIR,—During the past weeks there has been a good deal of correspondence in your columns about the relatively small number of people killed and injured while boxing, yet all the time far more people are involved in motor cycle accidents Time and again the story is the same boys and young men brought into hospital with head injuries so severe that it seems impossible that they will ever recover (in fact many do not)—and all this very largely because they were not wearing crash-helmets Surely, Sir, to make a motor-cyclist wear a crash-helmet is no more an infringement of his personal liberty than it is to make an industrial worker wear protective clothing or to make a ship's passengers do boat-drill If these young men will not take reasonable precaution to protect themselves of their own accord they must be made to do so by the community The law would be easy to enforce—one warning and then a summons

Worthing Hospital,
Sussex

P J G SIMONS

TRANSAMINASE ACTIVITY IN LIVER DISEASE

SIR,—We have read the two papers on this subject in your issue of June 14, and as neither of them refers to the work published by us since April, 1955, on the diagnostic value of serum-transaminase activity in virus hepatitis, may we briefly summarise our contribution to the argument?

Since our first papers[1 2] appeared we have been able to demonstrate that in virus hepatitis (1) both the aspartic- and alanine-ketoglutaric transaminase (that is to say, glutamic oxaloacetic and glutamic-pyruvic) activities of the serum show a remarkable increase (twenty to forty times), (2) the ratio (aspartic-ketoglutaric/alanine-ketoglutaric) becomes strongly inverted, falling from the normal mean value, in healthy subjects, of 1 24 to a mean value of 0 64, (3) this pattern is typical of virus hepatitis and is not generally found in any other of the hepatic, icteric, and anicteric diseases investigated (bacterial hepatocholangitis, hepatic cirrhosis, the liver of congestive heart-failure, occlusive jaundice, &c), (4) the aspartic-ketoglutaric/alanine-ketoglutaric ratio remains persistently inverted during recovery, when the absolute values of the serum-transaminase activities again reach almost normal levels, so that a retrospective diagnosis of virus hepatitis is often possible

All our subsequent findings,[3–6] as well as those of other workers, have confirmed our original statements

The inverted ratio can also be found in rare cases of occlusive icterus, hepatic neoplasm, and hepatic amœbiasis, but without the high enzyme activities of virus hepatitis, so that the enzyme pattern we described remains a valuable diagnostic test in this disease

The first data of Wróblewski and LaDue[7] on serum-transaminase activity in virus hepatitis were published in September, 1955—several months after our first papers—and dealt only with the aspartic-ketoglutaric transaminase Previously Wróblewski and LaDue[8] reported high aspartic-ketoglutaric-transaminase activity in clinical and experimental hepatic damage, but no numerical data were published, and no connection was mentioned with the diagnostic value of this determination in virus hepatitis Only in later papers[9–11] did

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1 De Ritis, F, Coltorti, M, Giusti, G *Boll Soc ital Biol sper* 1955, 31, 394
2 De Ritis, F, Coltorti, M, Giusti, G *Minerva Med* 1955, 46, 1207
3 De Ritis, F, Coltorti, M, Giusti, G *ibid* 1956, 47, 167
4 De Ritis, F, Coltorti, M, Giusti G *Rec Progr Med* 1956 20, 533
5 De Ritis, F, Coltorti, M, Giusti, G *Science*, 1956, 124, 32
6 De Ritis, F, Coltorti, M, Giusti, G *Clin chim acta*, 1957 2, 70
7 Wróblewski, F, LaDue, J S *Ann intern Med* 1955, 43, 345
8 Wróblewski, F, LaDue, J S *J Lab clin Med* 1954, 44 954
9 Wróblewski, F, LaDue, J S *Proc Soc exp Biol, N Y* 1956, 91, 569
10 Wróblewski, F, LaDue, J S *Ann intern Med* 1956, 45, 801
11 Wróblewski, F *Arch intern Med* 100 635

ANÆSTHESIA FOR THE EMPHYSEMATOUS

Sir,—I should like to endorse the plea by Dr Wynn and Dr Brooks (July 5) that anæsthetists should have facilities for obtaining not only the CO_2-combining-power but also the pH. A CO_2-combining-power of 65 vols % at a pH of 7.35 would be compatible with normality, but a CO_2-combining-power of 65 vols % at a pH of 7.25 would indicate uncompensated CO_2 retention. This acid-base balance of the venous plasma has been illustrated previously.[1]

Hull W. N. Rollason

LONDON MEDICAL ORCHESTRA

Sir,—I would crave the courtesy of your columns to bring to the notice of the musically minded the London Medical Orchestra, who are anxious to recruit players for the coming season starting in October.

There is something particularly enjoyable in the amateur orchestra and some great figures in our profession have found it a refreshing distraction, two who come readily to mind were His and Billroth (the friend of Brahms). Moreover, the present President of the Royal College of Physicians is at times observed performing valiantly in our ranks under the proficient conductorship of Doctor Ucko.

With the help of distinguished soloists this orchestra has raised over £400 this year for the Imperial Cancer Research Fund by public concerts, and will continue to help medical charities.

Dr E. V. Slaughter of 6, Oxford Court, London, W.3, would be glad to hear from any who are interested.

A. Dickson Wright
London, W.1 President, London Medical Orchestra

FLAMMABLE CLOTHING

Commenting on a discussion at the annual representative meeting of the British Medical Association in Birmingham this month, Mr S. G. Willby, press officer of the British Standards Institution (2, Park Street, London, W.1), writes:

It was disappointing to learn that the meeting saw fit to pass unanimously a Manchester motion expressing dissatisfaction with the report of a B.S.I. committee about flammable clothing.

It is indeed highly desirable, as Dr Marion Reekie, who sponsored the motion, said, that manufacturers should produce attractive flame-resistant clothing at prices only a little above those of normal garments. The report urges that this should be done. But it is a fact that at present all garments worn by children—apart from those made from certain of the synthetic fibres, from heavy woollen cloths, and from a few specially treated fabrics—are liable to catch fire. Our report sought to warn parents of this fact and of the contingent dangers.

It is a delusion to suppose that there exist two ranges of fabrics, one safe and the other dangerous. There are fabrics with flame-resistant finishes on the market, but research is still proceeding to devise finishes which will outlast the washing which every child's garment must undergo. And until shoppers demand and retailers stock these fabrics their prices are unlikely to fall appreciably.

What our report did bring out was that the design of garments may be fully as dangerous as their fabric. If a child wearing a nightdress stands close to an unguarded coal fire, up-draught may well suck the garment against the fire, and the child would be burnt even though the nightdress was made of flame-resistant fabric.

The campaign for guarding fires, which has now been vigorously taken up by the Government, is not in any way a substitute for the development of flame-resistant fabrics nor a concession to human frailty; it is a step towards preserving human life.

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[1] Rollason, W. N., Parkes, J. *Anæsthesia*, 12, 71.

Parliament

Doctors in Parking Meter Areas

In the House of Lords on July 5 Earl Howe asked the Government whether, in the rules governing the operation of parking meters in areas where they were installed, it was intended to make any special regulations to meet the needs of professional men, their clients, or their patients.—Lord Mancroft replied: No special provision for professional men, their clients, or patients was proposed by the local authority or included in the only parking meter order so far made—which is operating in North West Mayfair. Any local authority proposing such an order may include in it such exemptions under section 21 (4) of the Road Traffic Act, 1956, as they may wish, but I cannot anticipate the decisions of the Minister on any such applications. Earl Howe: Does not the noble Lord think that in the case of people, perhaps suffering from grave injuries, who are going to see their medical advisers, some relaxation of the parking meter regulations as they stand should be incorporated in any further order made for the same purpose?—Lord Mancroft: My Lords, it does not actually matter what I think. What does matter is what representations are made by the local authorities to the Minister when he has heard all the interests concerned. In the case to which I have referred I understand that no representations were made, and on the only other Order (from Marylebone Borough Council) before the Minister representations were made. The matter is still under consideration.

QUESTION TIME

Security at Broadmoor

In answer to a question Mr Derek Walker-Smith, Minister of Health, said that though he had not yet received the full report of the Board of Control inquiry into the recent escape from the institution he had received a summary of their main findings. They found that the saw used by the patient had been introduced into the institution from outside. They recommended that:

(1) Search of patients after visiting days should be intensified.

(2) There should be no exception to the rule that the siren is to be sounded immediately the escape of a dangerous patient is known.

(3) The strength of the night staff on duty in the block from which Mitchell escaped should be increased at once.

(4) Alterations to the walls of the institution to increase their security at strategic points should be commenced immediately.

They have already given instructions for the implementation of these recommendations.

Expenditure on Social Services

In 1956 the Exchequer spent £1554 million on the social services, the National Insurance funds £641 million, and the local authorities £704 million. The total, £2899 million, is 17.6% of the national income. The specific grants from the central Government to the local authorities are included in the Exchequer's contribution.

Tuberculosis Beds

In the past five years the number of hospital beds in England and Wales allocated to tuberculosis has fallen by 8935.

Emergency Morphine Supplies at Docks

After consultation between the Home Office and other departments, the Home Secretary has decided, as a special case, to authorise the keeping of supplies of morphine for use by nurses in an emergency at port medical centres where suitable safeguards can be arranged.

Merit Awards

The number of merit awards in payment in England and Wales at the end of 1957 was: 276 at the rate of £2500, 690 at the rate of £1500, 1377 at the rate of £500. The total amount paid is estimated at £1,450,000 in 1949 (the first full year) and £1,960,000 in 1957.

mentioned in the preceding letters are clearly less acceptable than others, but some in Dr Pappworth's list (ephebiatrics and ataralgesia, for instance) were coined for a clear purpose and are, we think, justifiable, though tentative, creations In the centenary year of Darwin's *Origin of Species*, it seems only decent to allow a little scope to Natural Selection —Ed L

SMALLPOX VACCINATION

Sir,—I have used the antecubital site for vaccination for more than ten years, and to the advantages mentioned by Professor Saunders (June 28) I would like to add one which, next to the cosmetic effect, appeals perhaps most to patients—that they can lie down in a bath resting the elbow on the sponge tray Furthermore, it is possible to sleep on that side, and the site is more easily protected in crowds, and is out of the way of those hearty fellows who greet one with an affectionate squeeze of the upper arm The only disadvantage is that in the case of a severe reaction the sling must be adjusted so that the angle of the elbow-joint is obtuse—a right-angle or less impedes the flow both in the veins and in the lymphatics

London, W 1 E G Huxley Cowen

5-HYDROXYINDOLEACETIC ACID IN STEATORRHŒA

Sir,—In your report of the meeting of the American Gastroenterological Association (June 21, p 1313) you quote the statement that the urinary excretion of 5-hydroxyindoleacetic-acid (5-H I A A) is increased in the patient with idiopathic steatorrhœa in relapse, but not in other types of steatorrhœa If this is confirmed it will be most helpful in the diagnosis of this condition, but a sprue-like state has been described in the carcinoid syndrome,[1] and I have recorded a case of idiopathic steatorrhœa, in which the diagnosis was confirmed by jejunal and ileal biopsy, with a normal urinary excretion of 5-H I A A [2]

Groote Schuur Hospital,
Cape Town Dennis M Krikler

DIASTOLIC PRESSURE AND MALIGNANT HYPERTENSION

Sir,—We have studied a group of 284 unselected hospital inpatients with hypertension, according to two scales of pressure (1) a scale of diastolic blood-pressure (D B P) divided into 6 " levels " of 15 mm Hg each, ranging from 85 to 160 mm and over, and (2) a scale of diastolic age-sex-adjusted-score (D A A S),[3] divided into 6 " degrees " of 15 mm each, ranging from 0 to 75 mm and over These two scales were correlated with the degree of change in the optic fundus, according to Keith, Wagener, and Baker, and with the frequency of electrocardiographic left ventricular hypertrophy, congestive cardiac failure, electrocardiographic coronary damage, and cerebrovascular accidents The ætiology of hypertension was not considered in this study

In the D B P scale 22% of the cases were over 130 mm (4th level) 26 5% of those with the malignant type of fundus were under 130 mm 83 3% of patients over 160 mm (6th level) had the malignant type of fundus, and none of the patients over 160 mm had a normal fundus

These figures were different in the D A A S scale 34 5% of cases were over 45 mm (4th degree), and only 10% of th with malignant type of fundus were under 45 mm Only 46 of patients over 75 mm (6th degree) had the malignant type of fundus, and 16 6% of cases over 75 mm had a normal fundus

According to this study, a diastolic pressure expressed in D A A S of 45 mm Hg (4th degree) marks the start of th malignant phase This level is more accurate than the classic D B P level of 130 mm The following table gives this malignant incipient level in D B P by age and sex

Age Men	10–13	14–25	26–38	39–51	52–70	71–84	
Women		10–23	24–34	35–43	44–54	54–64	65–81
D B P (mm Hg)	110	115	120	125	130	135	140

The D A A S makes it possible to identify patients with malignant hypertension before changes are evident in the fundus and before left ventricular hypertrophy develops It also allows the significance of high blood-pressure to be assessed in old people

The frequency of congestive failure and of left ventricular hypertrophy is related directly to the increase in diastolic pressure The frequency of the electrocardiographic coronary changes and of cerebrovascular accidents is not related to that increase

Aguirre Hospital,
University of Chile Ricardo Cruz-Coke

INTESTINAL ANGINA

Sir,—It is surprising to me that Dr Whiteside's letter of June 21 has passed without comment I believe that upper abdominal pain or discomfort or feelings of distension are not uncommon symptoms of ischæmic cardiac disease

Recently, one of these patients described her symptoms rather aptly, saying " When I walk fast I feel that I have too much air in my stomach, and none at all in my chest " She located her " stomach " about the centre of the epigastrium

A few months ago I saw an intelligent 38-year-old man who complained of a transient oppressive pain following severe exertion Electrocardiography suggested a small anterior cardiac infarct He was quite adamant that the location of his pain was not alone below the xiphisternum but was actually subumbilical

Limerick R Holmes

DEATH OF A BOXER

Sir,—I do not recollect that any of your correspondents so far has drawn a distinction between amateur and professional boxing When I was a member of my university boxing club 28 years ago the duration of an amateur contest was limited to three 2-minute rounds There is a vast difference between this and the professional contest of ten to fifteen 3-minute rounds towards the end of which muscular fatigue of the neck and trunk muscles must reduce the defence to a blow on the head Amateur boxing was then, and I presume still is, carefully controlled by a referee and two judges In my experience where there was an obvious discrepancy in skill the contest was speedily stopped

The suggestion of Dr Pakenham-Walsh (June 21) that because boxing is taught in schools and boys' clubs therefore professional boxing will continue to thrive seems to me a non sequitur I have personally only once watched professional boxing, and left nauseated after half an hour No doubt your correspondent draws on personal experience when he writes that wrestling is safer and more efficient, although I read in a newspaper report the other day of a wrestling match in which the rival contestants were removed unconscious from the ring

Manchester H Stuart Barber

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1 Waldmann, E B , Martin, W J , Ferris, D O *Proc Mayo Clin* 1955, 30, 127

2 Krikler, D M *S Afr med J* 1958, 32, 120

3 Pickering, G W High Blood Pressure London, 1955

tion that local authorities should be given more help from central funds for the development of their welfare services for the disabled, an allowance for this purpose will be included in the general grant which it is proposed to substitute in 1959–60 for the present specific grants The Minister also asks authorities who are not yet providing welfare services for the handicapped to reconsider the position He is aware that many of them are supporting the provision of these services by voluntary organisations, but he is satisfied that when the authorities themselves undertake this responsibility (in full cooperation with the voluntary organisations) more complete and uniform services can be given.

The Minister especially supports the Piercy Committee's recommendations for more hostels for the tuberculous and for convalescent mental patients and for short-stay accommodation for the elderly

DENTAL ANCILLARIES

The shortage of dentists is described as "universal", and in no country is the dental profession increasing as fast as the population. On the other hand, experience has shown that, by delegating part of their work to trained assistants, dental surgeons can look after many more people. For this reason the W.H.O Expert Committee on Auxiliary Dental Personnel, at their meeting held in Geneva at the beginning of this month, laid stress on the need for dental-health teams each supervised by a dentist using two or more assistants highly trained but in a limited field. Such teams (the committee think) could be introduced with advantage into the established dental programme of economically advanced countries as well as in building up services in areas which at present have little or no dental care.

Among the auxiliaries in the team, the committee include chairside assistants, dental technicians dental hygienists, and school dental nurses, but they recognise that the training and employment of such personnel will need to be graduated according to the particular requirements of the area. Since the auxiliaries—of whatever kind—must work under the direction of fully qualified dentists, who take responsibility for what they do, the committee recommend that attention should be given to the education of dentists in utilising the help of assistants

For areas where there is at present no professional dental service the committee propose the training of a special type of personnel At first, perhaps these could do no more than relieve pain and cope with emergencies, but they would also work in teams, and their training would be planned to allow for additional and continuing education as the service develops

The following are among the figures supplied to the committee by the International Dental Federation

Country	*Number of qualified dentists*	*Population*	*Ratio*
Australia	3900	2,125,000	1 2250
Canada	5564	16,589 000	1 2981
Germany	33,694	52,521,300	1 1559
Indonesia	300	80,000,000	1 270,000
Netherlands	2500	11,000 000	1 4400
South Africa	1250	13,500 000	1 10 800
United Kingdom	16,000	51,200,000	1 3792
United States of America	90,000	173 000,000	1 1900

Participating in the committee were Dr J Llewellyn Saunders (New Zealand), chairman, Dr James Deeny (Dublin), Dr A. I Domnikov (Moscow), Dr A. Maxwell Horsnell (London), Dr O K. Oswald (Gothenburg), Dr Shailer Peterson (Chicago), and Dr C. J Sundram (Penang)

LIGHT DIETS IN HOSPITAL

The Hospital Catering Advisory Service (King Edward's Hospital Fund for London) has issued a memorandum on "Light Diets". This term is vague and undesirable, but is still commonly used in hospitals to denote diets which are nutritious and easily digested but at the same time varied and tempting. Suitable recipes for soups, main dishes, puddings, and sauces are included.

Copies may be had from the Fund, 34, King Street, London, E C.2 (1s post free)

University of London

The title of professor of pharmacology and therapeutics has been conferred on Dr R. S Stacey in respect of his post at St. Thomas's Hospital Medical School, and the title of professor of pharmacology on Dr Eleanor Zaimis in respect of her post at the Royal Free Hospital School of Medicine. The title of professor emeritus of physiology has been conferred on Prof. K. J Franklin on his retirement from the chair of physiology at St. Bartholomew's Hospital Medical College.

University of Edinburgh

On July 17 the following degrees and diplomas were conferred

M.D—D L. Gardner (highly commended) E. N B Morton, J G Sommerville (commended), *J P Baird D S Harling, R. D Young

* In absentia

Ch.M—H. A. F Dudley (gold medal), J A. L. Clark (commended)

Ph.D—E. O Eracko

M.B Ch.B—Liselotte Adler F S-L. Ip, W J Irvine, B B. Porter (honours), Margaret E. Abel E. G Anderson, T Y Anderson Michael Andrews. A. D E. Atukorale, Keith Ballentyne. Jean E. Banyard. J D Bell D G Binns, Roelof Boersma L. R. Carner, J M Cochrane, W J C. Conn Alison R. Coutts. Joyce Cragg H. A Cumming W A. M Curling, I A. Davidson Elizabeth N Dawson J D Donnelly, Tessa N Dyke, Peter Edmond, Jenny R. Elder, J G Fegler, R. A Findlay, M H. Finlayson, E. P Fradin, Heather S Fulton, J M Gale. J B Gallacher, R. K Galloway, P J Garwood. Willa M Glover, A. S Goldstein, James Gollan E B. Gordon Norman Gordon. Christopher Grace, P J S Hamilton, Marion Hardman, William Hardy B M Henderson. Elsie M Hendry, D J Henry, J A. Hood. G R. Hopkinson, J E. Hugh Nesta B James, P D F James, J C. Jenkins, Ronald Kilgour Dorothy A. Lai Fook, Christine G Laing, C. A. R. Lamont William Leadbetter, D J Levy R. B Levy, K. T Lim J M McArdle, T R. McCall, Florence M McCallum, Harry McDonnell G A. McEwan, Katherine H. McEwen, R. S McGregor, C. L. K. McIlwaine Gordon Mackay Janette Millar J M Miller, A. R. Milne, A. R. K. Mitchell Kathleen M Moore, N H Munro. H M. Murray, J A. Ogunro, Lilian L. Orba, George Orr, W M. Paterson, Hilda Pedersen Christine A. Poole R. W Porter, I C. F Rach John Roberts, Denise E. Robertshaw D A. R. Robertson. K. D Robinson I S Ross, Mary C. D Ross, William Ryder, William Simpson, K B. Slawson. Arthur Sloan. A. G L. Smith. M. B. Smith F L. Smurthwaite, G J A. I Snodgrass R. H. Steele, P M Stell James Stevenson V. B Sumpson, E. L. R. Taylor, J M Thomas, E G Thomson Hilary Titterington D M Tod, W C. Uduku, T J Wallace, Sadie D Walsh A. G Watson, J A. G Watt, R. G Weeder, J P Welch, D W Welsh, A. E. Wightman. Christine Wileman. B J Wilken, Joyce M Williamson, R. S Wilson, Evelyn Wray, David Weinberg

D.P.H—J M W Bow Isabel J Buchanan, Bhailal Chaudhuri, M P Hutchinson Edith M. McLean David Penman J N Robertson, A. D Ross, J J Sawe, Edith Scott, J C. M. Sharp, G W Simpson, J A. K. Wallace.

D.T.M & H—Kollengode Ramaswamy Balasubramanian Nariman Kekobad Ginwala Vadakkepat Jayakumaran Sukumar Mukherjee, Thazhathuveetil Damodarapanicker Gopalakrishna Pillai. Braibans Prasad, Bhaskara R. Dodda, Kadavil Poulose George, Kudallur Raman Nambudiripad. Narendra Kumar Sinha.

D.M.R.D—S McC. Smith.

The Cameron prize was awarded to Prof Charles B Huggins, of the University of Chicago, in recognition of his researches on the hormonal treatment of cancer and particularly for his introduction of the treatment of prostatic carcinoma by oestrogens

Dr. K. W Donald reader in medicine in the University of Birmingham, has been appointed to the chair of medicine in succession to Sir Stanley Davidson, who retires at the end of March.

Dr Donald, who is 46 years of age, was educated at Emmanuel College, Cambridge, and St. Bartholomew's Hospital, qualifying in 1936 During the late war he served with the Royal Navy as senior medical officer with a destroyer flotilla and was awarded the D.S.O for his work in the Narvik action. In 1942 he created the Admiralty experimental diving unit and personally conducted investigations into survival in closed spaces, resuscitation, oxygen poisoning, and carbon-dioxide intoxication. Much of his published work has dealt with high-pressure physiology and cardio-respiratory function in health and disease. After the war he returned to Barts as chief assistant in the medical professorial unit. In 1948 he spent a year in the United States with a Rockefeller fellowship, and on his return he was appointed senior lecturer in medicine at the Institute of Diseases of the Chest, Brompton. In 1950 he became senior lecturer in medicine in the University of Birmingham and assistant physician to the Queen Elizabeth Hospital. Five years later he was appointed first assistant to the Birmingham chair of medicine. He is a consultant to the Royal Navy and chairman of the Under-Water Physiology Committee He is secretary of the Medical Research Council committee on breathing apparatus for protection against fumes and gases. He is also honorary consultant to the National Coal Board.

Dr J D Sleigh has been appointed lecturer in bacteriology

Obituary

EDWARD WALKER BAIN

M B *Lond*, F R C S

Mr Bain, honorary consulting surgeon to the ear, nose, and throat department of the Leeds General Infirmary, has died at his home in Arkendale at the age of 82

He qualified from the London Hospital in 1902, and after postgraduate study in Vienna took the F R C S in 1907 He held a senior clinical assistantship in the ear, nose, and throat department of the London Hospital and was for a time assistant surgeon at the Metroplitan Ear, Nose, and Throat Hospital before he was appointed to the staff of the Leeds General Infirmary in 1912 as the first surgeon of its new ear, nose, and throat department He was lecturer in E N T surgery at the University of Leeds and he also held appointments at St James's Hospital, Leeds, and at Castleford and Normanton During the first world war he served as captain in the R A M C, in the military hospital at Beckett Park, Leeds He retired from his hospital appointments in 1937, but during the late war he was recalled to his old department at the Leeds General Infirmary and he worked there until 1945

E S writes

As a surgeon, Mr Bain was careful, skilful, and deliberate A man of few words with a most equable temperament he was always courteous and dignified He had an extensive practice throughout the three ridings of Yorkshire, travelling far in the days of mastoid emergencies, and his advice was widely sought in consultations throughout the county

He had many interests outside his professional work, but gardening was his chief hobby During his later years he developed a great interest in fly fishing and he was a keen member of the Harrogate Fly Fishers Club He retired to the country, where he spent his last few years still much attached to his gardening Bill Bain will be mourned by all those who knew him, particularly residents and fellow consultants of the years after the first world war who will always remember his kindness and hospitality

Births, Marriages, and Deaths

BIRTHS

WOLFSON—On July 1, at Dudley Road Hospital, Birmingham, to Nancy, wife of L J Wolfson, F F A R C S—a daughter

Appointments

FORREST, D M, M B N Z, F R C S first assistant in general surgery, St George's Hospital, London
HOBDAY, T L, M B Lpool, D P H, D P A senior assistant port M O, Liverpool
MARRACK, DAVID, M D Lond assistant clinical pathologist, National Hospital, Queen Square, London
MURRAY, D S, F R C S E part-time consultant surgeon in orthopædics, Rotherham and Mexborough hospital group
OGILVIE, C M, M D Lpool, M R C P consultant physician, Liverpool Stanley Hospital
PAGE, F T, M D Lond, M R C P consultant physician, Bristol clinical area
QUINLAN, A G, M B Lond, F R C S consultant orthopædic surgeon, Scarborough hospital group and Adela Shaw Orthopædic Hospital, Kirby Moorside, Yorkshire
SLATTERY, J A, M R C S, D P H district M O H, Downham Market, Downham, and Marshland, Norfolk
TALLACK, R J K, M B Brist, D P H assistant M O H and school M O, Westmorland

Colonial Appointments

BENSON, T W, M B Lond M O, Jamaica
BERNARD F E P, M B Edin M O, Northern Nigeria
DAVIES, H N, O B E, M B Edin, D T M M O, Somaliland
DOYLE, V T B, M D N U I, M R C P I specialist, curative services division, Northern Nigeria
ECONOMIDES, A P, DIP MED Athens district M O, Cyprus
GILLETTE, G P S, M B Edin, D P H medical adviser, Federation of the West Indies
HAMERTON, J R, M B Lond, F F A R C S specialist anæsthetist, Uganda
McDOWALL, M F, M D McGill, D T M & H, D C H M O (grade A) pædiatrician Trinidad
MARGETSON, N E L M B Edin, D O M O, Jamaica
SOUTHGATE, B A, M B Lond M O Kenya
TEMPLER M J, M R C S M O, Kenya
THOMSON D M M, M B Brist M O Uganda
THOMSON, M J C, L M S S A M O, Uganda

Notes and News

MEDICAL SCHOOL FOR RHODESIA

ON Feb 1 we recorded some of the conclusions of the committee which is advising the University College of Rhodesia and Nyasaland on whether to set up a medical school The full report, now published as a supplement to the June issue of the *Central African Journal of Medicine*, points out that for the supply of doctors the Federation at present depends entirely on other countries

> "Apart from there being a limit to the extent to which a country can rely on borrowed talent, on the two counts of training and supply the situation is not becoming any easier while the demand is increasing In Great Britain there is one practising doctor to under 930 of the population, the corresponding figure in the Federation is one to approximately 13,000, but in ten years' time, if there is no considerable increase in the number of doctors, this already fantastic figure will have reached the level of one to 17,500 The number of doctors to the African population is very much less than the present over-all figure of one to 13,000—some put it at one to 37,000, and in one district at least (Mrewa) it is one to over 80,000 There is, moreover, a grave lack of full consultants to deal with the African population"
>
> "In two respects in which the medical services of the Federation are particularly at fault—maldistribution of medical personnel and lack of junior resident medical officers in hospitals—the advent of a medical school could bring about an immense improvement"

A new school should, it is suggested, be established within the next two or three years, with clinical teaching at the (suitably developed) African hospital at Harari, 7 miles from the University College at Salisbury It should at first have an intake of 25 students a year, and the course should lead to a qualification registrable by the General Medical Council

The members of the committee are Mr L Farrer-Brown (chairman), Prof W M Arnott, Prof T H Davey, Prof A D M Greenfield, Prof P B Medawar, Dr Honor Smith, and Prof R Milnes Walker

PIERCY'S RELIQUES

THE Minister of Health and the Secretary of State for Scotland have sent memoranda[1] [H M (58) 57 and S H M 58/54] to the hospital authorities drawing their attention to points in the report of the Interdepartmental Committee on the Rehabilitation, Training, and Resettlement of Disabled Persons[2]

The Minister asks the English boards to review their facilities and to consider what reorganisation may be desirable He suggests that they may find it convenient to begin by concentrating on two or three selected areas in their region. The matters which he would like to see included in the review are the general supervision and coordination of facilities, the assessment of disability, and the need for additional facilities, such as sufficient space for active physiotherapy, or, in the occupational-therapy department, for simple factory work or training for adjustment to home conditions In rural areas there may also be need for residential accommodation for selected patients who need a planned and fairly active convalescence

The Scottish report necessarily covers much of the same ground Also it suggests that each region should have at least one consultant who would give most, but not the whole, of his time to the rehabilitation service "He might advise the regional hospital board, be available to the specialists for consultation in difficult cases, and in his own unit undertake to pioneer the development of rehabilitation services" The Department of Health looks forward to the time when every major general hospital will have a rehabilitation department offering the full range of hospital facilities to outpatients A practical start, it thinks, might be made now with an experimental comprehensive rehabilitation and assessment centre

The Minister of Health in a memorandum to local authorities[3] says that, in view of the Piercy Committee's recommenda-

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1 See *Lancet*, 1956 ii, 986
2 See *ibid* 1956 ii, 986
3 Circular 16/158

The Lancet · Saturday 2 August 1958

THE TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

A REVIEW OF NINETY-THREE CASES

E J. WATSON-WILLIAMS
M B Camb , M R C P
LATE REGISTRAR, DEPARTMENT OF MEDICINE *

A I S MACPHERSON
Ch M Edin , F R C S E
SURGEON, EDINBURGH ROYAL INFIRMARY,
LECTURER, DEPARTMENT OF CLINICAL SURGERY

SIR STANLEY DAVIDSON
M D Edin , F R C P E , F R C P
REGIUS PROFESSOR OF MEDICINE

UNIVERSITY OF EDINBURGH

IN 1776 Werlhof described the purpuric condition now recognised to be associated with a deficiency in the number of circulating platelets Nothing that could influence the course of the disease was known until 1916, when Kaznelson reported a good result following splenectomy, and for the next thirty-five years this was accepted as the only effective treatment of idiopathic thrombocytopenic purpura After the introduction of corticotrophin and cortisone into clinical practice, it was observed that their use in high dosage was followed by improvement in some patients with this condition (Medical Research Council Hæmatology Panel reports 1952, 1953, 1955)

Material

93 patients (28 males, 65 females), in whom the diagnosis of idiopathic thrombocytopenic purpura was satisfactorily established, form the basis of this paper

Patients with thrombocytopenia associated with other hæmatological disorders or with portal hypertension, or following the use of drugs or other substances known to produce platelet deficiency, have been excluded All had hæmorrhagic manifestations and less than 100,000 platelets per c mm of blood on at least two occasions 85 patients had a prolonged bleeding-time, and of 70 in whom it was estimated, 58 had an increased capillary fragility Smears of bone-marrow were examined in 44 cases In all, the number of megakaryocytes was normal or increased, and no abnormality of the red cells or white cells was seen In no case was the spleen palpable, and the weight of spleens removed surgically ranged from 50 g to 230 g (average 120 g , which is within the limits of normal) (McNee 1931)

13 of the cases reviewed by Robson (1949) and 8 of those reviewed by Davidson et al (1952) have been followed up for a further period and are included in the present review 63 patients have been followed up for at least four years

Methods

Platelets were counted by the direct method in a counting-chamber, using capillary blood Since 1938, all examinations have been performed in the department of medicine of Edinburgh University, the great majority by one technician Normal values in this laboratory range from 200,000 to 500,000 per c mm of blood

The bleeding-time was measured either by Duke's method (Duke 1915) or by Ivy's method (Biggs and Macfarlane 1953) The normal range is from one to six minutes

Capillary fragility was estimated, in most instances, by the negative suction method (Scarborough 1941) Sometimes it was examined by the tourniquet method, the cuff being inflated to 100 mm Hg for five minutes The appearance at this time of six or more petechiæ within a circle 2 5 cm in diameter was considered abnormal

Throughout the series the method of *splenectomy* has been, with slight modifications, that practised by the late Sir David Wilkie

A few points deserve emphasis The stomach was emptied immediately before operation, and kept empty throughout by passing and retaining in position a stomach tube The incision usually made was left paramedian through or displacing the upper part of the left rectus muscle, but in a few patients with a wide costal angle an oblique incision was made in the line of the 9th or 10th intercostal space from the left anterior axillary line across the midline When the spleen was deeply placed or adherent, the lesser sac was entered through the gastrosplenic omentum to expose and ligate the splenic artery before beginning mobilisation of the spleen The spleen was brought forward and downwards by dividing from below upwards the lateral leaf of the lienorenal ligament and then the remainder of the gastrosplenic ligament containing the short gastric arteries After excision of the spleen, oozing from the raw area was reduced by suturing together the cut edges of the lienorenal and gastrosplenic ligaments, thus virtually covering the splenic bed with peritoneum If this is done, drainage is very seldom necessary, in fact it has been employed only twice An "anchored dressing" proved useful in preventing hæmatoma formation in the subcutaneous tissues

In the earlier cases in this series anæsthesia was induced with ethyl chloride and continued with open ether Latterly induction has been with intravenous thiopentone, and cyclopropane supplemented with relaxants has been used to maintain anæsthesia

Results

CASES GIVEN NO SPECIFIC TREATMENT †

No treatment other than whole-blood transfusion or hæmatinics was given to 26 patients, of whom only 3 were under 12 years of age They can be divided into two groups

The *first group* consisted of 10 patients who presented with a long history of recurring episodes of bleeding into the skin or from mucous membranes The bleeding was seldom severe and gradually subsided Throughout observation for periods as long as twelve years these patients have shown, in addition to episodes of bleeding, persistent (or in 1 case recurring) thrombocytopenia and a prolonged bleeding-time 3 have died—1 from gastrointestinal bleeding six months after the onset of symptoms, and 2 from causes unrelated to their thrombocytopenia five years and ten years after first being seen In only 1 case was there a clinical and hæmatological remission This lasted for two years, and followed a period of three years during which there had been repeated episodes of bleeding and persistent thrombocytopenia

The *second group* comprised 16 patients in whom purpura had appeared recently and without warning None had previously had a similar episode of bleeding

All 16 had crops of petechiæ in the skin and mucous membranes, 12 had persistent bleeding from the nose or gums, 5 had hæmaturia, 3 had gastrointestinal bleeding, and 5 had intracranial hæmorrhage—all females, of whom 4 died In every instance the bleeding-time was prolonged and the platelet-count below 50,000 per c mm , the capillary fragility was increased in 7 of the 8 cases in which it was estimated The 4 women who died did so within two days of admission to hospital Necropsy was performed in 3, and in each the cause of death was found to be intracranial hæmorrhage No other

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* Present address Department of Medicine, University College, Ibadan, Nigeria

† Throughout this paper the term "specific treatment" is used to denote steroid therapy or splenectomy

University of Durham

Dr N Cauna has been appointed to a readership in anatomy in the Newcastle division

University of Birmingham

On July 17, on the occasion of the British Medical Association's conference, the honorary degree of LL D was conferred on Lieut -General Sir Alexander Drummond, director-general, Army Medical Services, the honorary degree of D SC on Dr J S Mitchell, F R S, regius professor of physic in the University of Cambridge, and the honorary degree of M D on Dr I D Grant, president of the College of General Practitioners

On July 5 the following degrees were conferred

Ch M—K D Roberts, R W Tudor

M B , Ch B—A J G Campbell, F J Fawcett, Bernard Goodhead (*second-class honours*), T R Abbott, Ada M Adams, Derek Atkinson, Ann I Ballantine, A D Barnes, Ruth Barton, Vivien E Basco, L S Bernstein, Colin Berry, J E Bewley, Kishan Singh Bhogal, H E Black, A W Burdon, Brenda M Chant, A C Cottrill, D C Crawford, J T Davies, P W Davis, D G Emery, Sylvia D Gardner, Catherine M Gay, J R Geddes, Jean M Gibbon, Selwyn Glick, M G S Golby, I A Goldman, R W Griffin, R G Harrison, Frances E Heron, M J Hoare, G B Hunt, S E O Jones, Madmood Joomye, Menigha Kemmer (in absentia), A B Lavelle, Michael Lewis, Edna J Lloyd, Wendy I McNeilly, G L Morgan, Philippa N Mourant, M G Mullan-Feroze, Kenneth Newbold, D M Nicoll, E Aigbobasimi Oni-Okpaku, C E Oxnard, Doris H Pereira, C R Phillips, P R Preston, Susan E M Richards, C J Roberts, R N Smith, D B Southall, Sheila M Statham, Margaret S Taylor, C W Thompson, F R Walford, Albert West, Nora E Wild, T H Willets, P J Witherow, D A K Woodward

Royal College of Surgeons of Edinburgh

At a meeting of the college on July 15 with Prof John Bruce, the president, in the chair, the honorary fellowship was conferred on Prof Warren H Cole and Prof Isidore S Ravdin The following were admitted to the fellowship

S M S Ashraf, D W Blair, R C Buchanan, Peter Burgess, B N Chatterjee M C Chenoy, J S G Clark, J T F de Graft-Johnson, E J England, D S Grewal, W F Hasan, Grant Kerr, G C Liggins, John McLenachan, P S Mathur, Gunaratnam Muttuthamby, K N Nambudripad, K J O'Connor, S L Paton, G R A Raad, E F Reye, M C R Solling, J W W Thomson, Mary A T Tolley, M P Trivedi, D D Verma, R E D Williams, J S Winter, N K Yong

Faculty of Ophthalmologists

The following officers have been elected for 1958–59

President, Mr L H Savin, vice-presidents, Mr E G Mackie and Prof G I Scott, hon treasurer, Mr A McKie Reid, hon secretary, Mr E F King

Royal Society of Medicine

The following have been elected honorary fellows of this society

Mr L R Broster, Dr M G Candau, Prof William B Castle, Prof Andre F Cournand, Prof Denis Denny-Brown, Prof F de G d'Allaines, Prof Herwig Hamperl, Prof G Miescher, Prof Newell Philpott, Prof Georges Portmann, and Dr F Parkes Weber

Royal Society of Health

Fellowships have been conferred by this society on the following in recognition of their public-health work

Dr William Alcock, Dr E Michael Bluestone, Dr H D Chalke, Dr Richard J Dodds, Dr Philip Drinker, Mr G L C Elliston, Dr J A Gillet, Dr I A G MacQueen, Dr W H P Minto, Dr Pin Hin Teng, and Dr W H S Wallace

Diagnostic Centre for South London

The London County Council have appointed Brigadier H L Glyn Hughes, formerly senior administrative medical officer of the South East Metropolitan Regional Hospital Board, to be medical director of the proposed diagnostic medical centre at the Queen's Road Centre, Peckham The plans for this project were described in our issue of June 7 (p 1214)

Carlsberg-Wellcome Travelling Research Fellowships

The Carlsberg Foundation (Copenhagen) and the Wellcome Trust (London) announce a second series of awards of these fellowships which they jointly instituted in 1957 The successful candidates for 1958–59 are Dr S E Jensen and Dr D A T Dick

Dr Jensen of Kommunehospitalet, Aarhus, and Aarhus University, Denmark, will work in Prof Russell Fraser's department at the Postgraduate Medical School of London on the factors affecting serum-lipoids in man, and Dr Dick, from the department of human anatomy, University of Oxford, will work with Prof H Holter at the Carlsberg Laboratory on the osmotic properties of living cells

Medical Women's International Association

Proposing the toast of this Association at the banquet in London last Monday which concluded the eighth congress, Prof Stanley Alstead, P R.F P S, spoke of the character of women as a new dimension in medicine He was one of the host of men who say of women "How illogical How charming! How right!" The Association barred discussion of religion and politics, but not of philosophy, which brings to the world a measure of tranquillity The philosophy of women embraced æsthetics, and æsthetic values constituted in themselves an international language

Dr Esther Lovejoy, first president of the Association, traced its origin partly to the work of British medical women, —including the Scottish Women's Hospitals—in the first world war She also recalled a visit she paid, at Hastings in 1904, to Elizabeth Blackwell, the first woman doctor, who qualified in the United States in 1849 Dr Aitken, as former secretary and now president, expressed her belief in the usefulness of the Association with its 29 member and 3 observer countries

Prof Robert Platt, P R.C P, proposed The Medical Profession

He had been looking at passers-by in a London street, and, having been in medicine for quite a long time, had felt that he knew about the problems of many of them How lucky doctors were to deal with this wonderful succession of people—always interesting, however exasperating they might be The profession of medicine offered greater variety than any other, and in all its branches it was far more satisfying than ever before "beware of people who say that medicine isn't what it used to be, it never was" In Britain it must be practised largely in the context of the National Health Service, which had still not got over all its initial troubles "But beware of the people in Britain who tell you that they can't practise good medicine today They are the direct descendants of those who didn't practise it yesterday" The doctor-patient relationship had changed no doubt—but in no country more than in the U S A, where the change could not be due to the N H S The most important things could not be measured by science, and Professor Alstead's description of æsthetics as an international language reminded Professor Platt of a foreign 'cellist's remark to him "For the Ravel it is not enough to have skill One must also have love" This was equally true of medicine

Dr Katharine Lloyd-Williams proposed The Guests and Overseas Visitors—from all five continents

Responding, Dr Haldorsen said that Scandinavia has 650 members of the Association, and likened the purpose of its gatherings to that of a Scottish reel—"everybody meets everybody" Dr Del Mundo spoke of the 13,000 women doctors in Japan, Australia, and the Philippines, and of the welcome awaiting the Association at its Congress in the Philippines in 1962 Prof M L Chevrel, in expressing thanks for a hospitality which had freed the visitors from care, paid particular tributes to Dr Tosoni-Dalai and Dr Aitken, late president and secretary And Dr A D Morani, in both English and Spanish, replied for The Americas

Royal Medical Benevolent Fund

The annual general meeting of this Fund will be held at 11, Chandos Street, London, W 1, on Wednesday, July 30, at 5 P M

Regional-board Appointments

Dr H M C Macaulay retires on July 31 from the post of senior administrative medical officer to the North West Metropolitan Regional Hospital Board, and he will be succeeded by Dr F J Fowler Dr Fowler is at present deputy senior administrative medical officer to the North East Metropolitan Regional Hospital Board and he will be succeeded by Dr T A Ramsay

Dr Fowler, who is 46 years of age, graduated M.B from the University of Birmingham in 1935 After holding house appointments in Birmingham, he became in 1938 senior assistant medical officer at Derby City Hospital During the late war he served with the R A.M C in France, North Africa, and Algiers, finally serving, with the rank of colonel, as A D M S (administration) at Allied Force Headquarters On demobilisation in 1945 he was sent under the postgraduate training scheme to Hallam Hospital, West Bromwich, to work under Dr J H Sheldon In 1948 Dr Fowler was appointed assistant senior medical officer to the Oxford R H B He took up his present appointment in 1951 has now lasted for a year No improvement was observed in 2 patients (nos 1, 2) while they were receiving corticotrophin, but twenty days after stopping treatment there was a spontaneous remission. 3 patients (nos 9, 10, 16) obtained no benefit from steroid therapy and were submitted to splenectomy Of the other 8 patients, 1 (no 4) was given corticotrophin 30 mg daily for seventeen days, and thirteen days later experienced a complete remission, and 7 were treated with cortisone or prednisolone for three weeks or more 3 (nos 11, 12, 17) of these 7 patients had a complete remission starting at the end of the course of treatment and have remained well since, but 4 (nos 13, 14, 18, 19) did not benefit and were submitted to splenectomy

This group of short-history cases is a small one, for the condition is uncommon, and several of the patients have been treated with doses and for periods of time which would be considered inadequate by modern standards (Sturgis 1951) Nevertheless, in this group response to steroid therapy was not related either to dosage or to the duration of treatment, and in this respect our observations confirm those on idiopathic thrombocytopenic purpura reported by the Medical Research Council Hæmatology Panel (1953)

12 patients who were treated before 1949 and therefore did not receive steroids, and 7 who had failed to benefit from them, were submitted to splenectomy within a hundred days of the onset of symptoms (table II)

Operation was followed by a rise in platelet-count in 15 patients, of whom 13 have remained in complete remission for as long as they have been followed up and 2 (nos 4 and 15, table II) relapsed within three months 3 patients (nos 5, 7, 9), on whom operation was performed as an emergency because of the severity of their condition, received little or no immediate benefit, but started a complete remission between ten and forty-nine days later In 1 of these (no 7, table II) the platelet-count fell and symptoms recurred five weeks after splenectomy, but he improved rapidly on a small dose of prednisolone The remaining patient (no 19) did not show any rise in platelet-count and died from a cerebral hæmorrhage some six years after splenectomy 5 of the 7 patients in this group who failed to respond to steroids benefited clinically and hæmatologically from splenectomy

17 short-history cases have been observed for a year or more after splenectomy Repeated observations over periods from a year up to twenty-three years after operation indicate that a good clinical and hæmatological remission has been obtained consistently in at least 75% of short-history cases (table V)

Long-history Cases

36 patients received specific therapy more than a hundred days after the onset of symptoms

Corticotrophin, cortisone, or prednisolone was given to 23 patients (table III) In 3 cases (nos 1, 2, 3) this has been the only treatment given the other 20 patients have also been treated by splenectomy Steroid therapy was given to 11 patients only before operation, to 6 only after splenectomy had failed to relieve the condition, and to 3 both before and after operation

The results of steroid treatment, as judged by relief of symptoms and a platelet-count above 150,000 per c mm, were similar whether the patient received the steroids

TABLE III—LONG-HISTORY CASES TREATED WITH CORTICOTROPHIN CORTISONE, OR PREDNISOLONE

Patient	Age	Sex	Duration of symptoms (yr)	Treatment			Day platelets rose above 150,000 per c.mm.	Duration of platelet rise (days)	Length of follow-up (yr)	Progress
				Drug	Dose (mg)	Days given				
Cases treated with steroids alone										
1	33	F	3	Cortisone	100	12	7	4	5	Remission started 3 years later
2	26	M	20	Cortisone	100	9	—	—	5	Well when seen 5 years later
3	45	F	45	Corticotrophin	100	10				
				Cortisone	200	10	—	—	4	No improvement.
Cases treated with steroids followed by splenectomy										
4	38	F	12	Cortisone	100	12	—	—	4	Well.
5	29	F	2	Cortisone	100	15				
				Corticotrophin	160	10	—	—	5	Well.
6	40	F	5	Corticotrophin	100	14	10	4	—	3 months interval.
				Cortisone	100	21	9	11	—	1 month interval.
				Cortisone	100	10	9	—	6	Well.
7	72	F	6	Cortisone	150	22	—	—	3	No improvement.
8	66	F	1/12	Cortisone	200	10	8	2	1/2	Well
9	57	F	2	Cortisone	200	10	7	3	3	Well
10	16	F	3	Cortisone	300	10	—	—	2	Well
11	50	F	1/12	Cortisone	300	22	10	12	1	Well.
12	14	F	6/12	Cortisone	200	13	15	60	3	Splenectomy 1 year later
					300	15				
13	11	F	6	Cortisone	200	7	6			
					50	8	—	9	—	1 week interval
				Prednisolone	15	120	14	44	—	2 months interval
				Prednisolone	45	17	8	—	1/2	Well
14	28	M	12	Prednisolone	50	28	—	—	1/2	Well.
Cases treated with steroids after splenectomy only										
15	22	F	*1	Corticotrophin	100	10	—	—	6	No improvement.
16	30	F	*5	Cortisone	200	10	3	7	5	Purpura persists
17	36	F	*12	Prednisolone	50	21	12	39	1/2	Purpura persists
18	36	M	*10	Prednisolone	60	12	10	10	—	Course given for dental extractions
19	33	F	*1/12	Cortisone	100	10	—	—		No change in symptoms at any time.
					75	100			2	
20	38	M	*7	Cortisone	300	21				
					200	30	—	—	—	5 months interval.
				Prednisolone	50	21				
					40	5				
					15	200	—	—	1	No change in symptoms at any time.
Cases treated with steroids before and after splenectomy										
21	5	F	3	Cortisone	50	17	—	—	—	Well 3 years, then relapse
			*4	Prednisolone	50	16	6	46	4	Purpura persists
					10	270				
22	65	F	4	Cortisone	200	21				
					100	28	—	—	—	No improvement.
			*1/12	Prednisolone	60	22				
					20	39				
					10	360	—	—	1	No improvement
23	31	F	15	Cortisone	200	21	16	4	—	No improvement.
			*1	Cortisone	300	21	11	10	—	No improvement.
					50	100	—	—	1	1 year interval
			*2	Prednisolone	60	22	4	9	1/2	No improvement.

* Indicates that splenectomy had been performed this period of time before steroid therapy began.

TABLE I—SHORT-HISTORY CASES TREATED WITH CORTICOTROPHIN OR CORTICOIDS

Patient	Age	Sex	Duration of symptoms (days)	Treatment			Day platelets rose above 150,000 per c.mm.	Splenectomy	Length of follow-up (yr)	Progress
				Drug	Dose (mg)	Days given				
1	55	M	47	Corticotrophin	100	10	30		6	Well †
2	20	F	3	Corticotrophin	100	10	30		6	Well
3	32	M	30	Corticotrophin	100	3	3		6	Well
4	3	F	2	Corticotrophin	30	17	30		1	Well
5	33	M	2	Cortisone	100	4	4		5	Well
6	22	F	1	Cortisone	200	10	6		1/12	Well
7	59	M	3	Cortisone	300	8	4		3	Well
8	6	F	12	Cortisone	100	10	8		1	Relapsed immediately, but 30 days later started a spontaneous remission. Remains well
9	45	F	1	Cortisone	200	8	—	Yes	1	Cerebral hæmorrhage No change in symptoms until 49 days after splenectomy when platelets rose to and have remained at normal levels
10	26	M	21	Cortisone	200	10	—	Yes	1	Well
11	12	M	35	Cortisone	250	21	20		1	Well
12	29	M	1	Cortisone	300	21	21		1/12	Remains well on prednisolone 5 mg daily
13	31	F	6	Cortisone	200	20	—	Yes	3	Well
14	56	F	56	Cortisone	200	21	—	Yes	4	Well
15	69	F	21	Prednisolone	50	10	6		1	Well
16	40	M	4	Prednisolone	50	10	—	Yes	6/12	Severe hæmorrhage continued. Splenectomy followed 10 days later by [illegible] platelets Relapsed after 5 weeks
			*1	Prednisolone	20	12	10			Remission with steroids Now well.
17	14	M	2	Prednisolone	50	28	20		6/12	Well
18	62	F	7	Prednisolone	50	21	—	Yes	6/12	Melæna on 28th day Splenectomy Well
19	40	F	40	Prednisolone	60	24	—	Yes	1	Well

* 5 weeks after splenectomy

† In all tables the following terms are used
Well —Patient examined free of symptoms and platelet-count within normal limits
Presumed well —Patient reported by letter free of symptoms

disease was present The distinguishing feature of the other 12 cases was a spontaneous and apparently permanent recovery The hæmorrhagic phenomena stopped within fourteen days of admission, and concomitantly the platelet-count began to rise, becoming normal, in every case, within a hundred days of the onset of symptoms There has been no recurrence, and the patients have remained well for as long as they were followed up, which in 5 cases was for more than nine years

The existence of this second form of thrombocytopenic purpura, sudden in onset and short in duration, suggested to us the arbitrary division of our patients who were treated with corticotrophin, corticoids, or splenectomy, into (1) those in whom the onset was less than a hundred days before treatment started, and in whom, therefore, the possibility of spontaneous remission was still present (hereafter referred to as short-history cases), and (2) those with a history of more than a hundred days, in whom the possibility of spontaneous remission was slight (long-history cases) Hirsch and Dameshek (1951) selected a period of a hundred and twenty days, whereas Wintrobe et al (1937) thought that spontaneous remission was common before fifty days had elapsed but unusual thereafter Support is lent to our choice of a hundred days as the arbitrary dividing-line by the fact that 3 patients in this series have had between them 7 children who were born with thrombocytopenia and purpura and recovered spontaneously at varying intervals up to ninety days after birth A similar duration for this type of neonatal thrombocytopenia is recorded by Epstein et al (1950), Neville and Masterman (1954), and Schoen et al (1956)

It should be emphasised that the only factor taken into consideration in placing a patient in one or other of these two groups is the duration of *symptoms* before treatment was started The number or severity of hæmorrhagic manifestations, the degree of thrombocytopenia, and the prolongation of the bleeding-time have not influenced the classification

CASES GIVEN SPECIFIC TREATMENT

Short-history Cases

In 31 patients specific treatment was begun less than a hundred days from the onset of symptoms 19 patients were treated with corticotrophin (A C T H), cortisone, or prednisolone (see tables I and VI)

In 11 cases the duration of treatment was ten days or less There was complete remission of symptoms and a rise in platelet-count *to above 150,000 per c mm, which persisted after* treatment was stopped, in 5 of these patients (nos 3, 5, 6, 7, and 15, table I) In 1 patient (no 8) there was a temporary improvement, followed by a relapse when the drug was withdrawn and thirty days later by a spontaneous remission which

TABLE II—SHORT-HISTORY CASES TREATED BY SPLENECTOMY

Patient	Age	Sex	Duration of symptoms before splenectomy (days)	Previous treatment	Day platelets rose above 150,000 per c mm	Length of follow-up (yr)	Progress
1	18	M	2	—	1	8	Well.
2	31	M	4	—	1	12	Well 1 year No purpura Died from pulmonary tuberculosis
3	47	F	4	—	1	1	Well
4	27	M	7	—	1	3	4 weeks after operation platelet-count fell to 50,000 per c.mm. Remained low but symptoms improved.
5	45	F	9	Cortisone	49	1	No immediate response. Now well.
6	11	F	10	—	1	23	Well
7	40	M	14	Prednisolone	10	1/2	Delayed response Relapsed 5 weeks after operation Now well.
8	52	F	17	—	2	7	Well
9	54	F	20	—	23	9	No immediate response Now well
10	31	F	26	Cortisone	1	3	Well
11	62	F	28	Cortisone	1	1/2	Well
12	26	M	31	Cortisone	5*	1	Well
13	34	F	31	—	1	17	Well
14	30	F	40	—	1	9	Well
15	50	F	42	—	3*	15	Except for 2 periods of 2 years each platelets remained below 150 000 per c.mm
16	56	F	77	Cortisone	10*	4	Well
17	28	F	84	Cortisone	1	2	Well
18	19	F	84	—	8*	3	Well
19	55	F	91	—	—	6	Platelets always less than 50,000 per c.mm. Died from cerebral hæmorrhage

* This was the first day after operation on which platelets were counted.

observed to run a more chronic course (group B, table VII), two features emerge.

First, in group A the sex-incidence was 15 females and 13 males (1·15 to 1), whereas in group B it was 38 females and 11 males (3·5 to 1).

Secondly, the onset of symptoms in the cases with a short history was evenly spread throughout the age range, but in the group with a long history it was before the age of 30 in 37 of the 49 cases; in 7 of the remainder, all women, the onset was in the sixth decade.

For these observed differences in sex and age incidence in our two arbitrary groups of short-history and long-history cases, we can offer no explanation and we shall draw no conclusions from them.

Idiopathic thrombocytopenic purpura may present without previous warning as an episode of mild or moderate bleeding into the skin and from mucous membranes or as an illness which is serious either because of the degree of blood-loss or, as in intracranial hæmorrhage, because the site of bleeding is particularly dangerous. It is recognised that even when no specific treatment is given, spontaneous recovery can occur. However, serious symptoms may supervene even in mild cases at any time and especially in the first few days of the disease. 4 of our patients had intracranial hæmorrhage and died within two days of first being seen. The results of steroid therapy in our short-history cases suggest that these drugs do no more than facilitate the natural tendency of this disease to spontaneous remission and possibly accelerate its onset. Evidence from our cases about the place of splenectomy in the severely ill patient with a short history is equivocal.

3 patients (2 of whom were receiving cortisone at the time) were submitted to operation because of intracranial hæmorrhage or hæmatemesis. In none was there any immediate improvement, and 2 continued to bleed considerably, until all 3 recovered apparently spontaneously between ten and forty-nine days after operation. Another patient, in whom a diagnosis of intracranial hæmorrhage was made because of the sudden onset of dysarthria and monoplegia, was not submitted to operation and made a good recovery within three weeks.

On the other hand, there is convincing evidence of the beneficial effect of splenectomy once the acute hæmorrhagic phase has passed (tables II and V). Symptoms were immediately relieved, the bleeding-time was shortened and the platelet-count rose in 13 of the 14 patients of whom full records were kept; improvement persisted in at least 75% of cases followed up for more than twelve years after operation.

Our results suggest that the initial management of the patient with a short history of purpura should be blood-transfusion to replace any serious blood-loss and administration of cortisone (75 mg. every six hours) or prednisolone (15 mg. every six hours) for three weeks. If the platelet-count rises during this time, there is a very good chance that it will be maintained. If there is no improvement within three weeks, splenectomy should be performed in the expectation that at this time it will be followed by a good result in 75% of cases. We can adduce no evidence to show that the patient in the acute hæmorrhagic phase is benefited by splenectomy.

Patients with a long history of relapsing purpura should also be given a three-week course of steroid therapy. About half of all patients (table VI) improved during or shortly after treatment, but it is evidently exceptional for any such remission to last for more than sixty days. Therefore, it seems that all these patients should be submitted to splenectomy either during the steroid-induced remission or as soon as it is apparent that the treatment has failed to influence the platelet-count. However, when a remission does occur it may be justifiable to defer operation in milder cases, especially if it is a response to the first course of steroid treatment. Delay in these circumstances is probably harmless, provided the patient is able to report frequently for hæmatological examination so that the impending relapse can be anticipated and a further course of steroid therapy given as a preliminary to splenectomy. The chances of a permanent remission following splenectomy in this group of our patients, though less than in those with a short history, were still in the region of 50% up to twenty years after operation (table V).

Lundy (1953) has drawn attention to the danger of circulatory collapse during the induction of anæsthesia, and up to seventy-two hours after operation, in patients who have been treated with corticoids over long periods or who have received reduced amounts immediately before operation. No such collapse has been observed in our patients, but it is important to keep the patient fully under the influence of these drugs for seventy-two hours after splenectomy. Thereafter the dose can be reduced over a period of seven to ten days, but may have to be raised again to the initial high level should any complications arise after operation. In our series there have been no deaths in hospital after splenectomy, and com-

TABLE VI—EFFECT OF CORTICOTROPHIN, CORTISONE AND PREDNISOLONE

Drug	Dose (mg. per day)	Short-history cases			Long-history cases		
		Sustained remission	Temporary remission	No remission	Sustained remission	Temporary remission	No remission
Corticotrophin	30			1*			
	100	1		2*		1	3
		(4)	(1)	(3)		(6)	(4)
Cortisone	50–150	1	1*			2	6
		(2)		(2)		(3)	(2)
	200–300	4		4		7	3
		(2)		(1)		(1)	(1)
Prednisolone	15					1	
	45–60	2		3		4	3
Total		8 (8)	1 (1)	10 (6)	0 (0)	12 (10)	11 (7)

Figures in parentheses refer to cases reported by other workers (see text).
* These 4 patients subsequently had a spontaneous remission.

TABLE VII—93 CASES OF IDIOPATHIC THROMBOCYTOPENIA DIVIDED INTO GROUPS TO SHOW AGE AND SEX INCIDENCE

Age at first symptom (yr.)		0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Total
Short-history group (A)	Male	1	4	2	2	1	3	0	0	13
	Female	3	2	2	2	2	1	2	1	15
Long-history group (B)	Male	2	4	4	1	0	0	0	0	11
	Female	9	8	10	1	1	7	1	1	38
Unclassified because splenectomy was performed during first 100 days of disease	Male	0	1	1	1	1	0	0	0	4
	Female	0	1	2	2	2	3	2	0	12
Totals	Male	3	9	7	4	2	3	0	0	28
	Female	12	11	14	5	5	11	5	2	65

Group A comprises 28 patients: 16 who had no specific treatment, 12 who recovered within 100 days of onset and had received steroid therapy.
Group B comprises 49 patients: 10 who had no specific treatment, 33 who had splenectomy more than 100 days after onset, 3 who had splenectomy less than 100 days after onset and subsequently relapsed, 3 who had steroid therapy only more than 100 days after onset.

before splenectomy was performed or after it had failed (table III)

Thus 17 patients were treated with steroids before operation, with 8 remissions, and 9 after operation, with 5 remissions However, there is some evidence that higher doses of cortisone (over 200 mg per day) and of prednisolone (over 45 mg per day) were more effective A rise in the platelet-count and improvement in the clinical condition were observed during only 3 of 9 courses of treatment in which doses lower than this were given, whereas with the higher dose remissions were seen 11 times out of 18 In every instance both before and after splenectomy, the remission began within sixteen days of starting treatment, but in none did it last longer than sixty days On 7 occasions (nos 8, 9, 11, 16, and 23, table III) the relapse began while the patient was still receiving a large dose of the drug (either cortisone 200 mg per day or prednisolone 50 mg per day) 2 patients (*nos 21, 23*), who had responded to a large dose with a complete remission, were given long-term treatment with reduced doses, but both relapsed with symptoms comparable in severity to those before treatment was started. 3 other patients (nos 19, 20, 22), given long-term treatment, failed to benefit in any way

TABLE IV—LONG-HISTORY CASES TREATED BY SPLENECTOMY

Patient	Sex	Age at onset (yr)	Age at diagnosis (yr)	Previous treatment	Age at splenectomy	Length of follow-up (yr)	Progress
1	F	0–1	14	—	14	29	Remitting course Platelets 70,000 – 230,000 Symptoms improved.
2	M	0–1	5	—	5	1½	Died cerebral hæmorrhage.
3	F	0–1	20	—	20	5	Menorrhagia severe 2 of 3 children had thrombocytopenia
4	F	1	20	—	24	12	Menorrhagia severe
5	F	2	5	Cortisone	5	4	Well 3 years, then relapse
6	M	4	13	—	17	10	Well Killed on active service
7	M	5	5	—	6	9	Well
8	F	5	10	Cortisone Prednisolone	11	½	Well
9	F	6	9	—	14	9	Well 1 of 2 children had thrombocytopenia
10	F	11	11	—	13	5	Well
11	F	12	12	—	14	9	Well 2 years and reported well till died suddenly in relapse.
12	F	14	15	Cortisone	15	2	Well
13	F	16	16	Cortisone	17	2	Presumed well
14	F	16	25	—	25	10	Symptoms unchanged
15	F	16	30	Cortisone	31	2	Relapse after 2 weeks Severe menorrhagia continues
16	M	16	28	Prednisolone	28	½	Well
17	F	18	19	—	19	24	Well
18	F	21	22	—	24	23	Presumed well 7 years Relapse with severe *symptoms for past 16 years*
19	F	23	24	—	24	10	Well
20	F	25	25	—	26	3	Well until death from disseminated sclerosis
21	F	26	38	Cortisone	38	4	Relapse after 6 weeks Platelets below 50,000 per c.mm thereafter, but symptoms reported less
22	M	26	28	—	28	24	Known well 3 years Presumed well 21 years
23	F	27	29	Cortisone	30	5	Well
24	M	28	32	—	32	8	Severe symptoms *for* past year
25	F	30	31	—	31	12	Remitting course with platelets from 30,000–280,000 per c.mm.
26	M	33	35	—	38	11	Well
27	F	35	35	Cortisone Corticotrophin	40	6	Well
28	F	49	50	Cortisone	50	1	Well
29	F	52	53	—	53	2	Unchanged *Severe symptoms*
30	F	55	57	Cortisone	57	3	Well
31	F	61	61	Cortisone	65	2	Unchanged
32	F	66	66	Cortisone	66	½	Well
33	F	66	68	Cortisone	72	3	Relapse after 10 days

TABLE V—RESULT AT INTERVALS AFTER SPLENECTOMY

Period of observation (yr)	Short-history cases					Long-history cases				
	No	Traced	Well	Presumed well	% success	No	Traced	Well	Presumed well	% success
1	17	17	14	—	83	30	29	17	2	65
4	10	10	6	2	80	20	18	8	3	61
8	8	8	5	1	75	14	14	5	2	50
12	4	4	2	1	75	6	6	1	1	33
20	1	—	1	—	—	4	4	1	1	50

Splenectomy was performed in 33 patients with a long history of purpura—as the only specific treatment in 19 and after the administration of steroids in 14 (table IV) Follow up of these patients has shown that a year after splenectomy 19 of 29 patients (65%) were symptom-free and had platelet-counts and bleeding-times within the normal range, and that the proportion of those completely relieved declined to 61% at four years and to 50% or under between eight and twenty years after operation (table V)

In 22 patients the platelet-count was recorded within the first four days after operation It was within the normal range within twenty-four hours of splenectomy in 15 and within forty-eight hours in a further 2 The other 5 patients still showed thrombocytopenia on the fourth day, and in none of them was a normal platelet-count ever observed over periods of from one to twelve years after operation

Discussion

The results of steroid therapy are summarised in table VI

Almost half the patients with a short history of purpura (8 of 19) developed, during the course of treatment, a complete remission which was maintained after treatment was stopped In the group of patients with a longer history again about half (12 of 23) showed distinct improvement, but this was never maintained for more than sixty days This seemed such an important contrast that confirmation was sought in the reported experience of other workers (Bethell et al 1951, Fallon et al 1952, Jacobson and Sohier 1952, Meyers et al 1952, Stefanini et al 1952, Wilson and Eismann 1952, Adamson et al 1953, Greene et al 1953) Sufficient details to allow analysis were obtained for 32 patients (table VI) The results closely resemble those in our series In a further communication Stefanini (1955) said that permanent remission following steroid therapy was common among patients with a short history, but exceptional among those with a longer history of purpura The inference to be drawn from these observations appears to be that permanent remissions are not directly due to treatment with steroids, but may in some instances be hastened by it If this inference is accepted, it follows that the 12 patients among our short-history cases who entered a permanent remission during or shortly after treatment with corticotrophin or steroids (tables I and V), were examples of the self-limiting type of the disease, and in this respect are comparable with the 12 patients with a short history who recovered without steroid therapy or splenectomy

If these two groups of 12 patients, and the 4 who died without treatment within a short time of the onset of purpura, are considered together (group A, table VII) and compared with the 49 in whom the condition was nclair et al (1948a), repeating similar work with curate radiographic control of the position of the needle oint, suggested that it was the medial branch of the osterior primary division of the sensory root that was eing stimulated

There is also controversy about the more general neural mechanisms involved in referred pain The view put forward by several workers (e g Harman 1948) that reference is in part a cerebral event can hardly be denied, but this must play its part *after* more distal mechanisms have operated, and about these there is still conflict

One view (Mackenzie 1909) was that an "irritable focus" was produced at segmental level in the cord, with the result that sensation of pain from any part of the periphery of that segment spread to the central connections of all parts In its modern guise this has become the concept of a common sensory pool of neurones fed from skin, deep structures, and viscera in the appropriate segment (Hinsey and Phillips 1940, inclair et al. 1948b)

The other view considers that reference takes place at the periphery by misinterpretation of impulses coming up an axon which is branched and supplies both deep structures and skin, or by antidromic impulses passing down such a branched axon and producing chemical changes at the site of referred pain, or alternatively by a combination of both these mechanisms (Lewis 1942, Sinclair et al 1948b)

The physiological evidence on these two views has been assessed by Gordon (1975) Our observations may be relevant to, and derive added interest from, current theories of the mechanism of referred pain

Methods and Material

When 0 3 ml of 6% saline solution is injected as far as possible exactly into the midline of the back in the region of the interspinous ligaments at a depth of 2 or 3 cm, the immediate effect is stinging burning pain around the site of injection This is usually bilateral but may be more on one side than the other or entirely unilateral It subsides in one or two minutes, and, as it is subsiding, or after it has largely cleared, an unpleasant dull deep aching pain is experienced in the peripheral part of the segment injected and is sometimes accompanied by palpable spasm of the muscles of the segment Thus, for instance, when injections are made below the L5 spinous process, pain may be experienced in the shin, and spasm of the anterior tibial muscle may be felt The pain, although felt to be deep, can usually be clearly outlined by an intelligent witness

Sometimes accompanying this deep pain, and sometimes more delayed, a skin tenderness may develop, again mainly in the peripheral parts of the segment involved This hyperalgesia can become very severe and is similar to clinical hyperpathia in the skin area involved even the lightest touch may produce severe pain, ill defined in extent and hard to describe except as very unpleasant, but the raised threshold with subsequent overaction generally defined as hyperpathia is not in evidence

While this sensation lasts, the skin is carefully guarded from any contact, much as it is in causalgia This hyperalgesic effect is in our experience much less common than the others It may develop later than the deep pain and does not usually last longer than half an hour, whereas deep pain, described as vague muscle tenderness or a bruised feeling, may last as long as twenty-four hours or so after injection

All these effects may be unilateral or bilateral In our experience they are more commonly bilateral, especially in the cervical and thoracic regions, provided that the injection is made exactly in the midline Though some of these referred effects follow in most cases, occasionally none of them occurs and it must be emphasised that the only almost invariable accompaniment of the injection of saline solution is the local stinging pain

If, instead of 6% saline solution, 2% procaine is injected in the same way, there is occasionally produced a numb cold feeling referred mainly to the periphery of the skin of the appropriate segment There is a feeling also that the muscles underlying it are not responding with normal facility While this effect lasts, the sensory response to both cotton-wool and pinprick in the area changes both stimuli are considered to be less clear or less sharp It has been impossible, however, to test

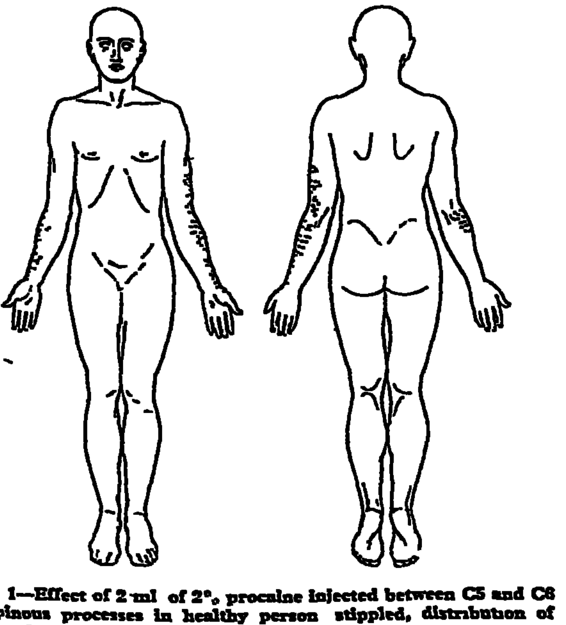

Fig 1—Effect of 2 ml of 2% procaine injected between C5 and C6 spinous processes in healthy person stippled, distribution of numb cold feeling

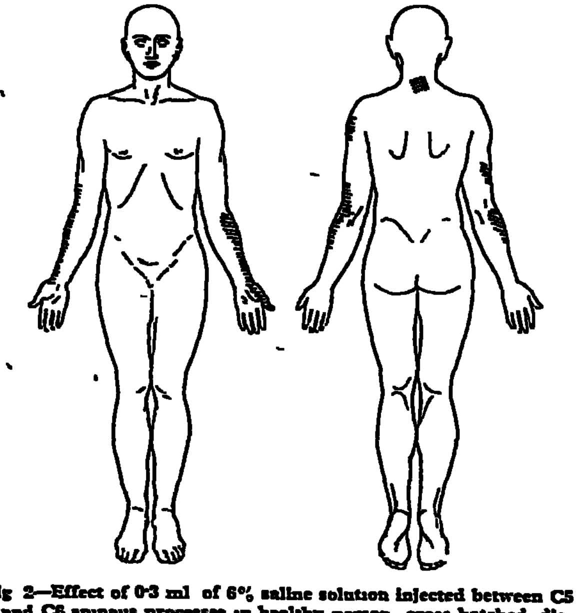

Fig 2—Effect of 0·3 ml of 6% saline solution injected between C5 and C6 spinous processes in healthy person cross-hatched, distribution of immediate stinging pain, hatched, distribution of deep aching pain

plications have been few and in general have been those that may follow any major upper abdominal operation

1 patient, who was drained at the time of the splenectomy, developed a left subphrenic abscess, which needed surgical treatment on the sixteenth day after operation She made a good recovery and was discharged home two months later In 3 cases subcutaneous hæmatomata led to partial separation of the wound edges, but in only 1 of these was further operation needed

Thus, in good surgical circumstances and provided the diagnosis of idiopathic thrombocytopenic purpura has been established by all means including the presence of megakaryocytes in bone-marrow smears, splenectomy is a safe operation and should not be unduly delayed However, patients with very mild symptoms, particularly if elderly, may remain relatively undisturbed by their thrombocytopenia for a long time 10 such patients have been followed up for periods of from three to ten years, and none of them has had symptoms sufficient to warrant admission to hospital, let alone to justify splenectomy In such cases a watching brief may be permissible

The management of the patient who continues to have severe symptoms after splenectomy is difficult Long-continued treatment with cortisone (75–100 mg per day) or prednisolone (10–15 mg per day) was given to 5 such patients in this series (and in higher doses to another operated on more recently) without any significant improvement in platelet-counts or in the severity of symptoms In contrast to these results, 2 of 4 patients who had failed to respond to splenectomy were treated by the Medical Research Council Hæmatology Panel (1955) with cortisone (50–100 mg daily) for more than six months and were maintained in remission for that time The details of these cases were not given and it may be that the 2 who were maintained had short histories and might, therefore, have remained well once a remission had been obtained—as did our case 16 (table I) Among the other reports in the literature we have failed to find an example of a patient with a *long history* of purpura having had a steroid-induced remission lasting more than two months (table VI)

The results of steroid therapy in our patients who relapsed after splenectomy (table III) suggest that if there is going to be improvement it will be evident within three or four weeks of the start of treatment, and will almost certainly not be maintained for much more than two months If the platelet-count has not risen within this time, it is unlikely to do so with further continuous treatment, no matter how intense or how long-continued It is better to stop treatment, accepting any minor clinical improvement that may have occurred, and to start another course should bleeding recur Whenever a minor operation or dental extraction is necessary in a patient with a persistently low platelet-count after splenectomy, it should be covered by a course of prednisolone starting four or five days before operation and lasting not less than ten days

Summary

93 cases of idiopathic thrombocytopenic purpura are reviewed

The progress of 26 patients who received neither steroid therapy nor splenectomy led us to classify the remaining 67 into two groups—namely, those who had a history of less than a hundred days from the onset of symptoms to the start of treatment (short-history cases) and those in whom this interval was more than a hundred days (long-history cases)

The response to treatment in these two groups described, and important differences in regard to prognosis and treatment are noted and discussed Short-history cases tended to remit spontaneously, and the onset of such a remission appeared to be hastened by steroid therapy Splenectomy was followed by good results in more than 75% of short-history cases in which a remission, spontaneous or induced, had not occurred. In long-history cases the chances of a spontaneous remission or of a lasting remission from steroid therapy are very small Splenectomy was followed by a good result in some 50–60% of long-history cases

Recommendations for the management of patients with idiopathic thrombocytopenic purpura are made

We wish to express our gratitude to all those physicians and surgeons in Edinburgh who have referred to us patients with purpura or have allowed us to include patients on whom they have operated—in particular to Sir James Learmonth, in whose charge most of the splenectomies were performed The help of our colleagues in the blood clinic and of Miss Sheila T Lindsay, B SC, who was responsible for most of the blood-counts, is also gratefully acknowledged

REFERENCES

Adamson, D G, Walker, W, McIntosh, A E (1953) *Brit med J* i,
Bethell, F H, Miller, S, Myers, M C (1951) *in* Proceedings of the 2nd Clinical Conference on A C T H (edited J R Mote), vol II, Therapeutics, p 173 Philadelphia
Biggs, R, Macfarlane, R G (1953) Human Blood Coagulation and its Disorders, p 348 Oxford
Davidson, L S P, Girdwood, R H, Swan, H J (1952) *Brit med J* i, 1059
Duke, W W (1915) *J Amer med Ass* 65, 1600
Epstein, R D, Lozner, E L, Cobbey, T S, Davidson, C S (1950) *Amer J Med* 9, 44
Fallon, W W, Greene, R W, Lozner, E L (1952) *ibid* 13, 12
Greene, R W, Fallon, W W, Lozner, E L (1953) *Amer J med Sci* 226, 203
Hirsch, E O, Dameshek, W (1951) *Arch intern Med* 88, 701
Jacobson, B M, Solier, W D (1952) *New Engl J Med* 246, 247
Kaznelson, P (1916) *Wien klin Wschr* 29, 1451
Lundy, J (1953) *Anesthesiology*, 14, 376
McNee, J (1931) *Lancet*, i, 1951
Medical Research Council Panel in Hæmatology (1952) *Brit med J* i, 1261
— (1953) *ibid* ii, 1400
— (1955) *ibid* ii, 455
Meyers, M C, Miller, S, Linman, J W, Bethell, F H (1952) *Ann intern Med* 37, 352
Neville, M L, Masterman, L M (1954) *Arch Dis Childh* 29, 163
Robson, H N (1949) *Quart J Med* 18, 279
Scarborough, H (1941) *Edinb med J* 48, 555
Schoen, E J, King, A L, Duane, R T (1956) *Pediatrics*, 17, 702
Stefanini, M (1955) *Arch intern Med* 95, 543
— Santiago, E P, Chatterjea, J B, Dameshek, W, Solomon, L (195 *J Amer med Ass* 149, 647
Sturgis, C C (1951) *in* Proceedings of the Conference on the Effects of Cortisone New York
Wilson, S J, Eismann, G (1952) *Amer J Med* 13, 21
Wintrobe, M M, Harvahan, E M, Jr, Thomas, C B (1937) *J Amer med Ass* 109, 1170

SOME ASPECTS OF REFERRED PAIN

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THE injection of hypertonic saline solution into the deep midline structures of the back produces both local and referred pain (Kellgren 1939, Lewis and Kellgren 1939) We have found this method of inducing referred pain useful both in investigating and treating cases of spontaneous pain of doubtful ætiology and in extending the clinical examination of loss of sensation of pain in certain known lesions of the central nervous system We report and discuss briefly here some observations made in such cases

Lewis and Kellgren (1939) considered they were stimulating the interspinous ligaments by their injections, but ensory loss is present from a cord lesion, it is still possible o get referred sensation by injecting hypertonic saline olution, but the sensation is modified

Case 2—A man, aged 22, dived into shallow water and ustained a crush fracture of the C5 vertebra After the immediate phase of spinal concussion had subsided, he had a Brown-Sequard syndrome with paresis of his left arm and leg and sensory loss to pinprick and temperature at the C6 segment and below on the right side There was also some posterior-column loss on the left paretic side The condition had been static for some years when he was examined

Injection of saline solution—Fig 3 shows the effect of injecting saline solution into the C7–D1 interspace There was immediate pain in the cross-hatched area only to the left of the injection site Some minutes later a typical dull aching pain developed in the hatched area in his left arm and hand Shortly afterwards, however, his right forearm experienced, in the dotted area which was within the area of spinothalamic loss, a tingling feeling which was neither painful nor unpleasant and was described as "like a tuning-fork" On another occasion he was given an injection of saline solution in the D6–D7 interspace The effect is shown in fig 4 Again the immediate stinging pain was felt just to the left of the injection site Then, during the next two or three minutes, there was a slow build-up of a bilateral unpleasant dull ache, felt as deeply placed and described as like being winded No skin hyperalgesia developed on either side The referred sensation was clearly felt on both sides, and even on direct questioning the patient denied any difference in intensity on the two sides

When the spinal cord is the site of a local lesion, this may also affect the site of reference of some of the sensations induced by the dorsal midline injection of saline solution, as case 3 illustrates Some of the effects noted in this case, although quite definite, are rare in our experience, we have only been able to produce them in one other case of spinal-cord lesion, though we have tried in several

Case 3—A boy, aged 20, was referred by the Army Medical Services because of difficulty in walking long distances

On examination he had a very slight spastic paraparesis There was a sensory level to light touch and pinprick at the D9 segment but no absolute sensory loss He had some degree of kyphus at the D7–D9 vertebræ. Laminectomy later showed a cord obviously stretched over the kyphus with some arachnoid adhesions at this level

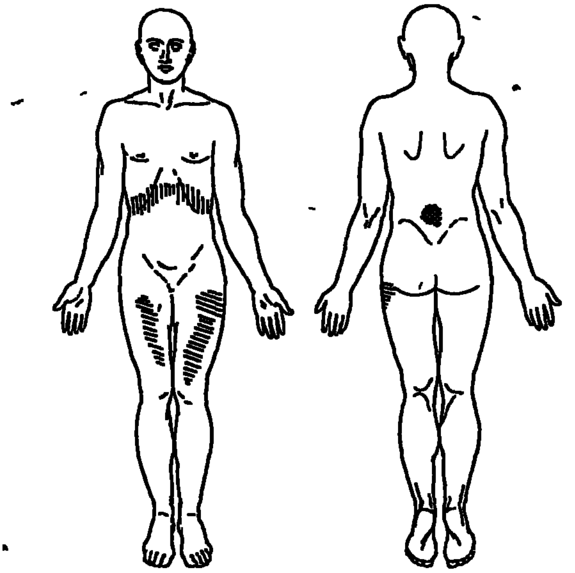

Fig 5—Effect of 0 3 ml of 6% saline solution injected between L3 and L4 spinous processes in case 3, with cord lesion and D9 sensory level cross-hatching, immediate stinging pain; transversely hatched, deep aching pain; vertically hatched, acute skin hyperalgesia

Injection of saline solution—The patient was tested with hypertonic saline solution some days before the operation Fig 5 shows the effects of an injection at the L3–L4 interspace There was immediate stinging pain in the cross-hatched area on both sides of the injection site As this subsided, a typical dull aching pain developed in the anterior parts of the thighs (hatched areas) There was no skin tenderness or hyperalgesia It was thought that the left quadriceps showed slight spasm to palpation The referred pain was more severe on this side than on the right The acute effect subsided in about ten minutes, and there remained only a slight feeling of muscle tenderness on the left However, about three-quarters of an hour after the injection there developed quite rapidly over two or three minutes severe hyperalgesia and tenderness of the skin over the epigastric region and lower rib margins (vertical hatching) So intense was this that the patient could not bear his pyjamas to touch the area and carefully held his clothes away from it, flinching at the slightest touch This intense effect lasted about ten to fifteen minutes and then gradually subsided Thirty minutes after the onset of the pain his skin was still hyperæsthetic to light touch, and pinprick felt unduly sharp, but these sensations were no longer unendurable, and he could button his jacket and tie his pyjama cord in comfort

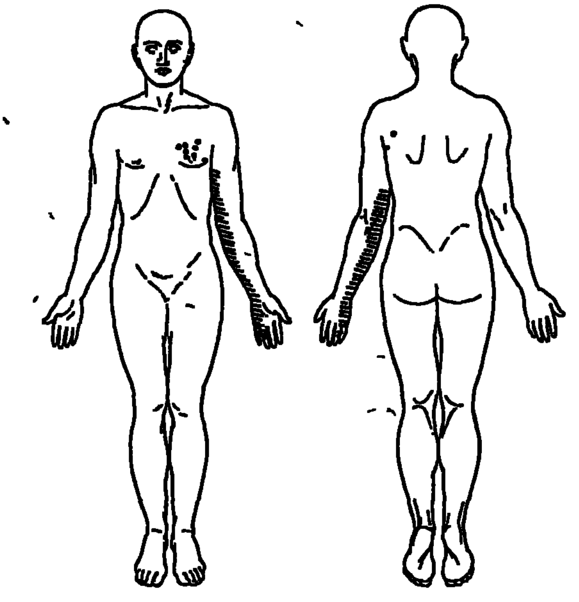

Fig 6—Case 4 with herpes-zoster scarring (small circles) and effort angina (hatched)

Case 4 illustrates that pain referred from a superficial focus in one segment may apparently summate with other potentially painful impulses not necessarily in the same segment The result may be pain referred to more than one segment This type of observation is not new Case 4 is of interest as illustrating some interconnection between three separate sources—pain of superficial origin, pain from deep somatic structures, and pain of supposedly visceral origin

Case 4—A woman, aged 64, had ten months' history of persistent post-herpetic pain After some prodromal symptoms a mainly D3–D4 herpes zoster had developed on the left side Vesication was slight and mainly on the anterior part of the body There was no secondary infection, and subsequent scarring was slight Nevertheless since the onset the patient quantitatively to determine whether sensory threshold has risen or not This effect is far less constant than that of the saline solution, and 1–2 ml of procaine has to be used to produce it

Fig 1 shows the effect of such a procaine injection in a healthy volunteer The effect was quite striking Although the volunteer had not been instructed in what he might feel he could outline readily the areas of sensory change produced The effect was clearcut only for fifteen minutes or so

Fig 2 shows the effect, on a different occasion in the same volunteer, of injecting 6% saline solution into the same area No skin hyperalgesia was produced, the hatched area representing the reference of deep aching pain Although roughly similar, the areas are neither strictly congruous nor entirely symmetrical Such variations and asymmetries are usual both with saline and with procaine injections

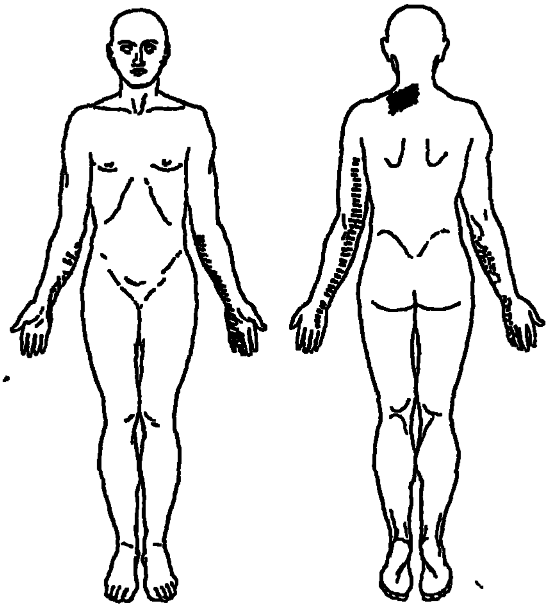

Fig 3—Effect of 0 3 ml of 6% saline solution injected between C7 and D1 spinous processes in case 2 with right spinothalamic loss below C8: cross-hatched, distribution of immediate stinging pain; hatched, deep aching pain; stippled, painless tingling

The production of referred hypoalgesia by procaine injections alone is inconstant, but, if saline solution is first injected and procaine is injected into the same site soon after the referred pain from the saline solution has come on, this pain is usually rapidly curtailed Equally, if pain is already present from a local lesion—e g, herpes zoster or a painful scar—procaine injected into the appropriate interspinous segment will often produce a sustained reduction in pain and hyperalgesia, this has useful clinical applications

Two points interested us in connection with these induced pains

(1) *How long after the saline solution has produced referred pain will a procaine injection into the same site abolish the referred effect?* The common referred effect—the deep aching pain—is usually waning spontaneously after ten to fifteen minutes, but in a milder form it may last much longer So far we have produced a pronounced and rapid change in the referred pain by injecting procaine up to five minutes after the injection of saline solution Our usual procedure is to leave the saline needle in situ and to inject procaine through this, but in so cases the analgesic effect has been produced by a separ injection into the same or a very nearby site

(2) *Will anæsthesia of the site of referred pain abolish pain?* Conflicting evidence has been produced on this po when the question of skin pain referred from a visceral sou has been investigated Several workers have reported relief pain by anæsthesia of the referred site (Weiss and Davis 19 Morley 1931), whereas others have been unable to achieve t (Woollard et al 1932, Livingston 1943) Possibly this appa contradiction is partly due to a lack of distinction betwe referred pain and the less common referred skin hyperalgesia tenderness Lewis (1942), for instance, suggested that t mechanism of these two might differ, the hyperalgesia depend on axon reflexes, and the pain on defective localisation A som what similar view was put forward by Wolff and Wolf (194 However, the suggestion of Doran and Ratcliffe (1954) that t cord centre for summation of impulses from two sources ha threshold above which reference occurs, may be a more sat factory explanation, because local skin anæsthesia may th only sometimes reduce summated impulses below thresho level The following case is relevant to this problem

Case 1—Here saline-induced unilateral referred ach pain and skin hyperalgesia both occurred in the C7 segme "freezing" the hyperalgesic skin with ethyl-chloride sp both abolished the hyperalgesia and greatly reduced t referred aching As the effect wore off, apart from the transi perversion of sensation that always follows local ethyl-chlor anæsthesia, the hyperalgesia did not return and the dull ac also remained less These later effects may simply have be the natural waning of the referred sensations, but the imm diate effect was striking and occurred when the sensations we obtrusive and at their height

The mechanism of anæsthesia by freezing must differ fro that of nerve block, but in this setting it has the advantage th muscle and other deep afferents cannot be involved as th may with infiltration anæsthesia We can therefore argue th whatever effects are seen are those of alteration of skin sensati alone, whether by simple blocking of stimuli or possibly al by "bombardment" from an intense cold stimulus

The two following cases illustrate the ways in which t effects of injecting hypertonic saline solution may altered by spinal-cord lesions When spinothalam

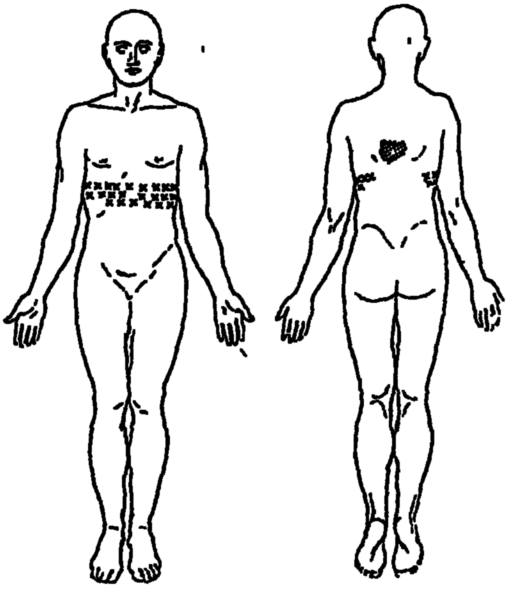

Fig 4—Effect of 0·3 ml of 6% saline solution injected between and D7 spinous processes in case 2 cross-hatched, distribution immediate stinging pain; small crosses, deep aching pain

(3) Any view of the neural mechanism involved in referred pain will have to try and explain all the facts At present there is a dichtomy of views into those concerned with peripheral mechanisms (such as pattern of peripheral sensory innervation, axon branching, and antidromic impulses) and those postulating a more central mechanism (such as a common sensory neurone pool in a segment of interconnected segments of the cord) This dichotomy seems unnecessary There is no reason why each mechanism should not be involved in some of the effects noted, nor indeed why both should not be involved together

Summary

The induction of referred pain by hypertonic saline solution injected into the interspinous ligaments and of referred hypoalgesia by similar injection of procaine in a healthy person is described

The modification of such referred phenomena in cases of spinal-cord lesions is described and discussed

A case of post-herpetic pain with referred phenomena and their modification by interspinous saline and procaine injections is described and discussed

This paper was read by one of us (C W M W) to the section of neurology of the Royal Society of Medicine, and we have to thank the honorary editors of the society's *Proceedings* for permission to publish

REFERENCES

Doran, F S A , Ratcliffe, A H (1954) *Brain*, 77, 427
Gordon, G (1957) *Proc R Soc Med* 50, 586
Harman J B (1948) *Brit med J* i, 188
Hinsey, J C , Phillips, R A (1940) *J Neurophysiol* 3, 175
Kellgren, J H (1939) *Clin Sci* 4, 35
Lewis, T (1942) Pain London
— Kellgren, J H (1939) *Clin Sci* 4, 47
Livingston, W K (1943) Pain Mechanisms New York.
Mackenzie, J (1909) Symptoms and their Interpretations London
Morley, J (1931) Abdominal Pain Edinburgh
Nathan P W (1956) *J Neurol Psychiat* 19, 88
Sinclair, D C , Feindel W H., Weddell, G , Falconer, M A (1948a) *J Bone Jt Surg* 30-B, 515
— Weddell, G , Feindel, W H (1948b) *Brain*, 71, 184
Weiss, S , Davis, D (1928) *Amer J med Sci* 176 517
Wolff, H G , Wolf, S (1948) Pain Springfield, Ill
Woollard, H H , Roberts, J E H , Carmichael E A (1932) *Lancet*, i, 337

LEUKÆMIA. DOUBTS AND DIFFICULTIES

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While engaged in a survey of the data on leukæmia contained in the records of the Ministry of Pensions and National Insurance (Abbatt and Lea 1957, Lea and Abbatt 1957) we have been much impressed by certain fundamental uncertainties the true incidence of leukæmia in the general population, the apparent increase in the death-rate from leukæmia in the general population in 1911–55, and the identification of the various types of leukæmia We attempt here to estimate the extent of these doubts

True Incidence of Leukæmia in General Population

In any disease which is not compulsorily notifiable the only evidence on which an estimate of its incidence can be based is provided by the certified death-rate In many diseases the death-rate can give no information about the incidence, but leukæmia is so extremely fatal that the death-rate must approximate very closely to the incidence If, therefore, it could be assumed that all cases of leukæmia were diagnosed, very probably no serious error would be introduced by taking the death-rate as the incidence

Unfortunately there is no guarantee that all cases of leukæmia are diagnosed, nor do we know of any method of estimating the size of the discrepancy There seems to be little doubt that an unknown proportion of cases diagnosed either as aplastic anæmia or as agranulocytosis are cases of leukæmia in an aleukæmic phase We have found 119 cases so diagnosed in the records of the Ministry of Pensions and National Insurance, which contain copies of the full notes, both Service and civilian, and in 18 of these (15%) we think the diagnosis is doubtful Our reasons for these doubts range from pathological reports—e g , " The predominating cell is not a typical lymphocyte but rather bigger with scanty cytoplasm, it lies somewhere between a lymphocyte and a lymphoblast, a few are definitely lymphoblasts "—to frank statements—e g , " The possibility that the aplastic anæmia may have been preceded by an aleukæmic type of myeloid leukæmia cannot be completely ruled out " At this date it is too late to do anything more than express doubts about these cases Even if pathological specimens were obtainable, it seems very unlikely that any firmly based conclusions could be reached

An unknown proportion, almost certainly small but sufficiently large to affect the apparent incidence of leukæmia, of adults over middle age certified as dying from cerebral hæmorrhage have no doubt died in that way, but the cause of the hæmorrhage has been leukæmia and not cardiovascular disease Similarly, some cases of acute leukæmia in infancy may be confused, in the absence of hæmatological investigation, with various acute infections

On the other hand, it seems very improbable that a death will be certified as due to leukæmia unless hæmatological investigation has been made No such case was found in our 691 cases from the records of the Ministry of Pensions and National Insurance It therefore does seem legitimate to conclude that the death-rates from leukæmia given by the Registrar General (1912–56) for 1911–55, do not err in the direction of overestimation, and that the rates given can be regarded as minimal

However, it does not follow that this will continue to be so The publicity recently given to the effects of radiation and the occurrence of leukæmia in irradiated cases of ankylosing spondylitis, goitre, persistent thymus, &c , must have produced some degree of " leukæmia-mindedness " in the medical profession In what direction, and to what extent, such a state will affect the certification of death from leukæmia it is impossible to say, but some effect seems to be inevitable Because of this we are of the opinion that the certified death-rates from leukæmia for the next few years are likely to be unreliable

Apparent Increase in Death-rate from Leukæmia in 1911–55

Since 1911 there has been a great increase in the apparent death-rate from leukæmia For males of all ages, the death-rate per thousand living in England and Wales in 1911–15 was 0 012 and for 1951–55 0 053 The corresponding figures for females were 0 010 and 0 043 (R A M Case and J T Pearson, unpublished) The male rate has increased 4 4 times and the female 4 3 This suggests that the factors responsible for the increase apply equally to both sexes These apparent increases, however, have not been uniformly distributed over the various age-groups, the greatest changes being in infancy and had had severe pain, felt in the skin in the affected dermatomes and deeply beneath it, almost entirely anteriorly The area rapidly developed a typical protection hyperalgesia, and when seen she could not endure even the lightest touch to the affected area without experiencing severe, diffuse, and intensely unpleasant pain Apart from this she had a mild hypertension She did not complain spontaneously of any symptoms referable to her cardiovascular system, but on direct questioning she described effort angina It appeared as a slight feeling of substernal constriction and an aching pain referred down the left arm rather diffusely, but more ulnar than radial It could be induced fairly consistently by walking briskly twice round the ward It subsided within a few minutes of resting Fig 6 shows the distribution of pain and the site of her zoster scarring

Intercostal block —The patient was given an intercostal block of 2% lignocaine to the D3 and D4 spaces About 10 ml was infiltrated in the posterior axillary line The post-herpetic pain was immediately reduced The hyperalgesia was abolished and the skin could be handled without discomfort The effect lasted about an hour and a half During this time the patient discovered that she could walk round the ward without inducing her usual anginal pain This was put to the test and although she had the usual slight breathlessness she was emphatic that she had no arm pain

Interspinous injection —In the routine treatment of her post-herpetic neuralgia she was given procaine into the D3 and D4 interspinous ligaments This relieved both the herpetic pain and the angina, the effect lasting about two hours On another occasion hypertonic saline solution was injected into the D3 and D4 interspinous sites This produced some increase in the herpetic pain and considerable aggravation of the hyperalgesia at the edges of the scarred area The anginal pain was not induced, however, and her usual exertion, undertaken when the herpetic pain was aggravated, did not produce any arm pain After repeated saline plus procaine injections to the D3 and D4 interspinous areas over a period of some days post-herpetic pain and hyperalgesia were permanently reduced Local massage and vibration to the scarred area were made possible, and with this she has remained comfortable for a six-month follow-up period

Discussion

The response of saline-induced pain to procaine injected at the saline site shows that referred pain, after its inception, may still depend on impulses from its primary activating focus If chemical change at the site of reference is responsible for it, such change must be very labile and maintained in some way by the primary focus

Anæsthetising the skin over the region to which pain is referred also appears to modify the referred pain, as shown in case 1 This is not incompatible with the previous observation if one assumes that part of the mechanism of reference is a summation of sensory inflow in the cord In that case reducing *any* impulses which pass to the centre of summation may reduce the referred sensation

A similar problem is posed by the observations in case 4 Weiss and Davis (1928) reported temporary abolition of angina by anæsthetising the area of skin reference In case 4, however, even if we assume a post-fixed brachial plexus, anæsthesia of an area of painful skin a segment or two away abolished the anginal pain Even when the painful skin area was rendered hypoalgesic as a referred phenomenon from anæsthesia of deep midline structures in the same segment, this also reduced the anginal pain It is difficult to imagine anything more peripheral than a cord mechanism being responsible for this The fact that temporary exacerbation of the herpetic pain by saline injection seemed to reduce anginal pain is also compatible with a cord mechanism in which stimuli may compete for a common afferent pathway, but competition for cerebral representation (Lewis 1942, Doran and Ratcliffe 19 would also explain it

The abolition of referred skin hyperalgesia, as dis from pain, by anæsthetising the site of reference, wh is also illustrated in case 1, is to be expected because t hyperalgesia is elicited by stimulation of the affected sk

Mackenzie (1909) emphasised that it was almost alw pain that was referred, rather than any other sensati This has at times been used as an argument that refere is largely psychological In case 2 there was clear reference of sensation to both sides of the body in the segment, but on the side served by the damaged spin thalamic tract the sensation was not painful This sugges that conduction and redistribution of impulses occur i the cord, whatever more peripheral mechanism is involv In case 2 also referred sensation which *was* painful w felt on both sides of the body at the D6 level, but it differ in quality from the pain felt in the upper limb As a res of the cord lesion in case 2 the appreciation of pain an temperature in the skin and pain from the compress of skeletal muscle were absent on clinical testing of t right side It therefore seems that the pathways in th cord for these sensations may differ from those subser the unpleasant sensation that this patient experien bilaterally

Kellgren (1939) and others have described a delaye onset to referred pain and hyperalgesia and have pointe out that reference is sometimes only approximatel segmental The hyperalgesic episode in case 3 was qual tatively similar to those occasionally observed at the site referred pain and aching following the midline injectio of saline solution in healthy people However, in case it was referred some six segments away from that of th saline injection, moreover it appeared at the upper lev of the clinical sensory deficit It is difficult to escape th conclusion that this delayed referred sensation involve a spinal-cord mechanism in its mode of reference and wa in some way bound up with the cord lesion suggested b the clinical findings Nathan (1956) describes a simil reference of pain beyond segmental limits in cases bot with and without lesions of the spinothalamic tract H also considers that this reference takes place at spinal-cor level, and he discusses in detail the possible anatomic and physiological basis for it The time sequence in case is also of special interest because a mechanism apparentl activated by the saline solution took up to three quarter of an hour to manifest its clinical effects

In conclusion we emphasise three points

(1) The clinical implications of these induced referred pai and other effects have still not been fully explored The application may be therapeutically rewarding, but (perhap more important) the methods can readily be applied to health people to give a wider and potentially more valuable field study

(2) It must be accepted that the response to hyperton saline solution varies Occasionally there may be no referr effect at all The same effect cannot always be reproduced the same person even with seemingly identical technique Th structure of the nervous system, the activity of the sens neurone pool, learnt and innate reactions to pain, and, partic larly, the patient's powers of observation may all introdu variations and apparent discrepancies The facts are large what the patient says he feels, and accurate description is n always easy for him The need for such accuracy is illustrate in the confusion between referred pain and referred hype algesia which has certainly arisen at times Nevertheless furth observations in this field are clearly worth while and will n doubt establish an agreed body of facts

type was changed during the course of the illness in 102 (16 2%) Of these 102 cases 72 were acute (as defined above) and 30 chronic. Of the 630 cases 370 were acute and 260 chronic, hence the changed diagnoses occurred in 19 5% of acute cases and 11 5% of chronic It is generally agreed that great difficulties exist in determining the cell type in many acute leukaemias, hence we were not surprised to find differences of opinion in such cases We were particularly surprised to find differences of opinion in so many chronic cases

The details of the changes in diagnosis of the cell type were as follows

Diagnosis on Peripheral Blood		*Diagnosis on Peripheral Blood*	*No of cases*
Myeloid	to	Lymphatic	4
Myeloid	to	Monocytic	2
Lymphatic	to	Myeloid	12
Lymphatic	to	Monocytic	4
Monocytic	to	Myeloid	4
Monocytic	to	Lymphatic	2
Diagnosis on Peripheral Blood		*Diagnosis on Sternal Marrow*	
Myeloid	to	Lymphatic	2
Myeloid	to	Monocytic	2
Lymphatic	to	Myeloid	13
Lymphatic	to	Monocytic	3
Monocytic	to	Myeloid	3
Diagnosis on Sternal Marrow		*Diagnosis on Sternal Marrow*	
Myeloid	to	Lymphatic	1
Myeloid	to	Monocytic	2
Lymphatic	to	Myeloid	1
Diagnosis on Sternal Marrow		*Diagnosis on Peripheral Blood*	
Myeloid	to	Lymphatic	1
Diagnosis on Blood and/or Marrow		*Necropsy Diagnosis*	
Myeloid	to	Lymphatic	2
Myeloid	to	Monocytic	1
Lymphatic	to	Myeloid	9
Lymphatic	to	Monocytic	3
Monocytic	to	Myeloid	3
Monocytic	to	Lymphatic	1

In 1 case lymphatic leukaemia was diagnosed on lymph-node biopsy and changed to myeloid at necropsy, but certified as lymphatic. 1 case was only diagnosed at necropsy as leukaemia of uncertain type and certified as lymphatic leukaemia 1 case was diagnosed on peripheral blood as ? lymphatic, ? monocytic leukaemia, and as myeloid at necropsy In 16 cases three diagnoses were made 9 of these reverted to the original diagnosis, but in the 7 others all three possible diagnoses were made.

Six changes of diagnosis are possible, and all of them were made myeloid to lymphatic 10, myeloid to monocytic 7, lymphatic to myeloid 35, lymphatic to monocytic 10, monocytic to myeloid 10, and monocytic to lymphatic 6

Equally remarkable was the finding that in 30 cases the diagnosis on the death certificate differed from the necropsy or haematological diagnosis. This is a singular finding

The evidence provides no grounds for regarding the second or third diagnoses as preferable to the first. In most of these cases no doubts were expressed about the original diagnosis Most of the changes were made when the patient was moved from one hospital to another and reinvestigated. These findings necessarily throw much doubt on the value of the diagnoses in those cases in which the patient was not transferred. The question must arise would there have been a change in the diagnosis of cell type if the patient had been investigated in another hospital? It cannot be emphasised too strongly that, although these cases of leukaemia occurred in members of the Forces, the great majority of the investigations were made in the civilian hospitals of this country It should also be realised that most of the diagnoses were made by general pathologists and not by haematologists, and that though these findings are generally applicable to the United Kingdom they may differ from the results of the highly selected sample that would be obtained from teaching hospitals

It is clear that we cannot accept our findings on the change in cell type during the past fifteen years as having any real meaning A change may be taking place, but the possibility of wrong diagnosis is far too great for this to be anything more than a suggestion It is also evident that any attempt to draw conclusions from the cell type given on death certificates is quite unjustifiable at present.

The remedy for this unfortunate position is not for us to discuss, but it is evident that the confusion on the type of leukaemia is very widespread A case of particular interest in this respect was one in which, after full haematological investigation, the patient was, with complete notes, transferred to another hospital and at once reinvestigated on the grounds that the clinical picture did not fit the haematological one. In view of the uncertainty about cell type which we have shown to exist such a statement seems to have little justification but it certainly indicates a very confused state of affairs

Summary

The deaths from leukaemia given in the Registrar General's Statistical Reviews are unlikely to be over-estimates

Although some of the apparent increase in the death-rate from leukaemia in 1911–55 is due to improvement in diagnostic facilities, the greater part of it appears to be real

The diagnosis of cell type in leukaemia is, at present, too unreliable for conclusions to be drawn from it, this particularly applies to conclusions drawn from death certificates

We are indebted to Prof J V Dacie and Prof L. J Witts for helpful advice and criticism in the preparation of this paper, and to the Chief Medical Officer of the Ministry of Pensions and National Insurance for permission to publish data taken from the records of the Ministry

REFERENCES

Abbatt, J D, Lea, A. J (1957) *Lancet* ii 917
Case, R. A. M. (1956) *Brit J prev soc Med.* 10, 172.
Collins, E. T, Mayou, M. S (1925) Pathology and Bacteriology of the Eye. London.
Lea, A. J Abbatt, J D (1957) *Lancet* i, 389
Price, F W (1922) A Textbook of the Practice of Medicine. London.
Taylor, F (1914) Practice of Medicine (edited by E. P Poulton) London.
Registrar General (1912–1956) Statistical Review of England and Wales London.

IMPORTANCE OF STAPHYLOCOCCUS AUREUS IN PNEUMONIA IN THE 1957 EPIDEMIC OF INFLUENZA A

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IN Sheffield the epidemic of influenza, due to the Asian variety of influenza-A virus, was at its height in September and October, 1957 In these two months 140 patients with pneumonia were admitted to the general medical wards of this hospital

We review these cases here and discuss some factors that affected prognosis The association between influenza-A virus and *Staphylococcus aureus* (coagulase-positive) is well recognised, and we emphasise the

TABLE I—RESULTS OF BACTERIOLOGICAL EXAMINATION OF SPUTUM AND NECROPSY MATERIAL IN 140 CASES

Organism	No of cases
Staph aureus	38 (*27%*)
Pneumococci	12 (*9%*)
H influenzæ	5 (*4%*)
Friedländer's bacillus	7 (*5%*)
β-Hæmolytic streptococci	2 (*1%*)
Coliform bacilli	10 (*7%*)
No significant organisms	65 (*46%*)
No bacteriological examination	1 (*1%*)
Total	140

importance of this organism both as an early and as a late bacterial invader

Methods

A retrospective study was made of the case-notes and laboratory records for the months of September and October The criterion for inclusion in the series was evidence of consolidation of the lung demonstrated by either radiography or necropsy

In the laboratory each sputum was cultured aerobically on a horse-blood agar plate Necropsy material was cultured on a blood-agar plate both aerobically and anaerobically and on a MacConkey agar plate The plates were read after overnight incubation at 37°C In the interpretation of cultures the presence of bacterial pathogens, especially *Staph aureus*, was reported only when they were considered to be present in significant numbers It has been found in this laboratory that the use of a heated blood ("chocolate") agar plate did not appreciably increase the isolation-rate of *Hæmophilus influenzæ*, so long as small colonies, especially those showing satellitism in the presence of staphylococci, were fully examined Most of the necropsy specimens, however, were cultured on chocolate-agar as well as on blood-agar

Staph aureus was identified by the slide and/or the tube coagulase test, pneumococci by their sensitivity to ethylhydrocupreine ('Optochin') *H influenzæ* by satellitism around a colony of *Staph aureus* on a blood-agar plate, and coliform bacilli by colonial morphology All organisms were checked for their morphological appearance When pathogenic bacteria were not isolated, the result was recorded as "no significant organisms"

Sensitivity was tested by placing antibiotic discs on a blood-agar plate inoculated with the organism on the surface, and the results were read after overnight incubation at 37°C The organisms were tested against aureomycin, penicillin, streptomycin, chloramphenicol, erythromycin, and sulphonamides, and were recorded as being either sensitive or resistant

Results

The results of the culture of sputum and necropsy material are set out in table I, which shows that *Staph aureus* was isolated from 27% of the cases and pneumococci and *H influenzæ* from only 9% and 4% respectively

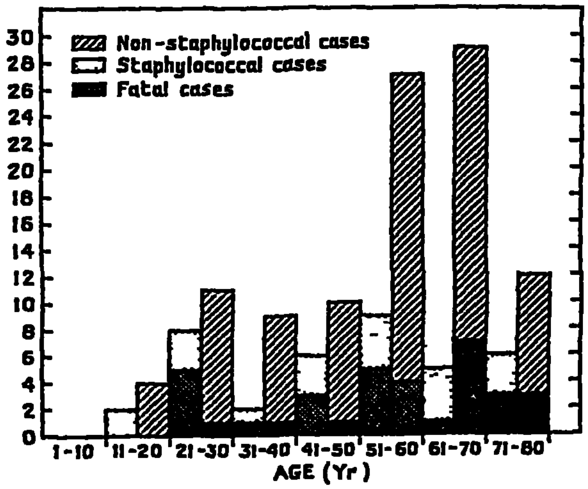

Fig 1—Age-distribution and mortality in staphylococcal and non-staphylococcal pneumonia

The cases can be divided into two large groups those in which *Staph aureus* was isolated, and those in which it was not

The incidence and mortality, by age, in the staphylococcal and in the non-staphylococcal groups are given in fig 1 In the staphylococcal group there were 38 cases with 18 deaths, a mortality of 47%, and in the non-staphylococcal group there were 102 cases with 16 deaths, a mortality of 16% The overall mortality of the series was 24% There was no clear sex difference in either group

A further comparison of incidence and mortality, in relation to pre-existing disease, is set out in table II Two large groups may be noted—one with no pre-existing disease and the other with chronic chest disease There are four other small groups which are too small for comparison In the two larger groups the mortality was much greater when *Staph aureus* was present

TABLE II—COMPARISON OF INCIDENCE AND MORTALITY IN STAPHYLOCOCCAL AND NON-STAPHYLOCOCCAL CASES ON THE BASIS OF PRE-EXISTING DISEASE

Clinical state	Non-staphylococcal group		Staphylococcal group	
	Total no	No of fatal cases	Total no	No of fatal cases
No previous disease	35	2 (*6%*)	19	8 (*42%*)
Chronic chest disease	48	8 (*17%*)	13	7 (*54%*)
Hypertension and ischæmic heart-disease	5	3	1	1
Pregnancy	4	0	2	1
Pregnancy and mitral-valve disease	3	1	1	1
Rheumatic heart-disease	7	2	2	0
Total	102	16 (*16%*)	38	18 (*47%*)

An analysis of the sex distribution according to age shows that males predominated in the older age-groups, because of the high incidence of chronic chest disease in this area The relatively larger number of females in the younger age-groups may be due to the more serious prognosis of postinfluenzal pneumonia in pregnancy and rheumatic heart-disease

There were 33 cases of pneumonia in women of child-bearing age (16–40), 10 of these were pregnant, 8 being in the third trimester (table II)

13 patients had valvular heart-disease, 11 of them having lesions of the mitral valve Of these 11 patients with mitral disease 9 were females, and 3 died (all females)

The antibiotic sensitivity of the strains of *Staph aureus* isolated from the 18 fatal cases are presented in table III Antibiotic-sensitive strains are those sensitive to aureomycin, chloramphenicol, penicillin, streptomycin, erythromycin, and sulphonamides Antibiotic-resistant strains are those resistant to aureomycin, penicillin,

TABLE III—ANALYSIS OF ANTIBIOTIC SENSITIVITY OF STRAINS OF *Staph aureus* ISOLATED FROM 18 FATAL CASES

No of days in hospital	Antibiotic sensitive strains	Antibiotic resistant strains
<1	9	0
2–7	3	2
8–14	0	2
15–21	0	1
22–28	0	1
Total	12	6

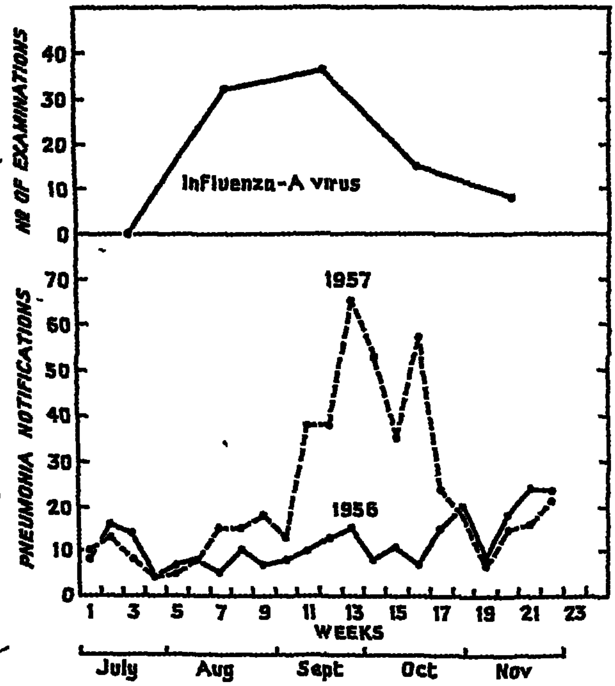

Fig 2—Pneumonia notifications to M O H, Sheffield, in 1956 and 1957 and numbers of cases in which influenza-A virus was found.

streptomycin, and sulphonamides and sensitive to erythromycin and/or chloramphenicol Erythromycin was the only one of the six antibiotics used in the laboratory routine to which all the strains of *Staph aureus* were sensitive

The culture results and the sensitivity of strains of *Staph aureus* isolated on admission to hospital and in hospital are shown in table IV

Discussion

The number of cases of infection with influenza-A virus diagnosed in the Public Health Laboratory, Sheffield, from all sources, is set out in fig 2, which also gives the number of pneumonia notifications to the medical officer of health, Sheffield, in September and October in 1956 and 1957 Fig 3 gives the admission-rate, by weeks of the 140 cases under discussion.

The results of the virus study reflect, to some extent, the prevalence in the community of infection by influenza-A virus These results, in conjunction with the increase in pneumonia notifications in September and October, 1957, compared with the previous year, and in conjunction with the admission-rate of the 140 cases to hospital, tend to support the view that most of the cases under review were, in fact, of postinfluenzal pneumonia Serological evidence of infection with, and isolation of, influenza virus A was made in a proportion of the cases Many of the patients gave a history of a typical influenzal illness preceding the pneumonia

The viruses of influenza B, C, and D (Sendai virus) were not detected in the community in comparable periods in 1956 or 1957 Influenza virus A was not detected in the autumn of 1956

The fact that most of the patients had been given antibiotics before admission to hospital may explain the large number of cases (46%) in which cultures of sputum and necropsy material did not reveal any pathogenic bacteria (table I) This supposition is supported by the 10 cases (7%) in which coliform bacilli were isolated from sputum, because these bacilli are often isolated from sputum cultures made during or immediately after antibiotic therapy

TABLE IV—ANTIBIOTIC SENSITIVITY AND RESISTANCE OF STRAINS OF *Staph aureus* ISOLATED ON AND AFTER ADMISSION TO HOSPITAL

No of patients with	No of survivors	No of fatal cases
Antibiotic-sensitive strains isolated on admission and thereafter	7	12
Antibiotic-sensitive strains isolated on admission, with antibiotic-resistant strains isolated later	2	0
No significant organisms isolated on admission, with antibiotic-sensitive strains isolated later	0	0
No significant organisms isolated on admission, with antibiotic-resistant strains isolated later	8	3
Antibiotic-resistant strains isolated at first bacteriological examination	3	3
Total	20	18

Thus the bacteriological results in this series are not directly comparable with any of the series in the pre-antibiotic era, because many of the pathogenic organisms —e g, pneumococci and *H influenzæ*—may have been killed or had their growth suppressed If we accept that the low isolation-rates for pneumococci and *H influenzæ* (9% and 4% respectively) were due to the use of antibiotics before admission to hospital, the isolation-rate of *Staph aureus* (27%) may be lower than the true incidence Stuart-Harris (1953) found that *Staph aureus* was isolated from 20% of cases during an influenzal period and from 4% of cases during a non-influenzal period

In the Public Health Laboratory, Sheffield, during 1955–57 the percentage number of sputa from which *Staph aureus* was isolated increased during influenzal epidemics (L Robertson and J E M Whitehead, to be published)

The greater severity and mortality of the cases infected with *Staph aureus*, along with the prevalence of the organism in sputa during influenzal periods, suggest an association between the organism and the virus Whether this is an additive or a synergistic effect is open to speculation

Of the cases infected with *Staph aureus* there are two groups large enough for comparison (table II) In the "healthy group" there were 19 patients of whom 8 (42%) died, whereas in the "chronic chest group" there were 13, of whom 7 (54%) died As would be expected, the average age of the "chronic chest group" was higher than that of the "healthy group" owing to increasing prevalence of chronic bronchitis in the older age-groups In 13 of 61 cases (21%) in the "chronic chest group", and in 19 of 54 cases (35%) in the "healthy group" *Staph aureus* was isolated from either sputum or necropsy material

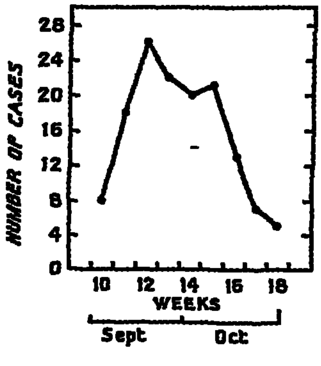

Fig 3—Distribution of admissions of 140 patients with pneumonia to hospital

Of necessity the patients admitted to hospital were selected Those who had previously been healthy were admitted because they had a serious illness Several had the syndrome of " peculiar cyanosis " and " gelatinous exudate " described by French (1920) Necropsy in these cases showed necrosis, in whole or in part, of the tracheobronchial epithelium The trachea and bronchi were bathed in bloodstained purulent material Microscopy showed numerous gram-positive cocci, and pure growths of *Staph aureus* were obtained on culture There was considerable pulmonary œdema, a thin serous bloodstained fluid exuding from the lungs on pressure 1 patient presented the appearance of toxic myocarditis In the " chronic chest group " the infection often precipitated respiratory or cardiac failure, and in the fatal cases in this group necropsy revealed more often changes of a conventional pneumonic pattern However, some tracheal and bronchial subepithelial hæmorrhage was present in most cases

The hospital environment is contaminated with *Staph aureus* With the increasing use of antibiotic and chemotherapeutic agents strains resistant to several such agents can be isolated from the noses of members of the hospital population, blankets, superficial skin lesions, &c In a disease such as influenza, where a possible association between the virus and *Staph aureus* can be shown, there may be a danger in introducing a patient with a postinfluenzal pneumonia not due to *Staph aureus* into such an environment It is thought that hospital infection did take place in this series Thus, an analysis of the antibiotic sensitivity pattern of the strains isolated from all the cases of staphylococcal infection shows that 21 cases (table IV) had sensitive strains on admission to hospital, and that 2 of these later acquired a resistant strain There were 11 patients from whom *Staph aureus* was not isolated on admission to hospital but who subsequently showed evidence of infection with resistant strains Most of the resistant strains were isolated after the first week in hospital, three of these were isolated after the temperature had subsided and the patients were recovering from the infection No cases became superinfected with sensitive strains in hospital

Table III, where the antibiotic sensitivity of the strains of *Staph aureus* isolated from the 18 fatal cases is presented, shows that, in cases which were fatal within twenty-four hours of admission to hospital, all the strains isolated were sensitive to aureomycin, chloramphenicol, penicillin, streptomycin, erythromycin, and sulphonamides—i e, the patients were infected with strains having the antibiotic sensitivity pattern that one would expect to find outside the hospital community From the second to the seventh day after admission to hospital there were 5 deaths From 3 of these 5 patients antibiotic-sensitive strains were isolated, from the 2 others antibiotic-resistant strains were isolated post mortem, no previous bacteriological examination having been made In all, there were 6 fatal cases infected with resistant strains, and in 3 of the 6 cases resistant strains were isolated from the first specimens examined Possibly the 3 patients were infected with antibiotic-resistant strains before entering hospital, but such strains are not commonly found outside the hospital community These infections may well have been acquired while these patients were in hospital

An example of infection in hospital with antibiotic-resistant strains of *Staph aureus* was seen in one of the wards where 7 patients with pneumonia were admitted From 3 patients *Staph aureus* phage-type 77 was isolated, and these three strains, which were not present in the first specimen of sputum examined, were sensitive to erythromycin and chloramphenicol only From the 4 other patients antibiotic-sensitive strains were isolated, one strain was type 53, one type 52A, and the two others were not typed

Bacteriophage typing of *Staph aureus* was done on strains isolated from 16 cases There was no predominant type

The treatment of the fulminating staphylococcal infections is very difficult, because it is necessary to treat both the bacterial infection and the attendant pulmonary œdema and peripheral circulatory failure 14 such patients died within the first week of admission to hospital, and all had been treated in hospital with massive doses of antibiotics, including erythromycin and chloramphenicol Despite this treatment antibiotic-sensitive strains of *Staph aureus* were isolated from 12 of the patients post mortem In contrast the less severely affected patients responded well to antibiotics, and those infected in hospital with antibiotic-resistant strains responded well to the antibiotics indicated by the in-vitro sensitivity tests

In hospitals where patients are being treated with antibiotics the nasal flora is suppressed, and it is possible that the nares can then become colonised by the antibiotic-resistant strains of *Staph aureus* present in the hospital environment Gould and Cruikshank (1957) have successfully suppressed *Staph aureus* in the nares with antibacterial creams Possibly hibitane, combined with either neomycin or bacitracin, as a nasal cream, as they suggest, would be of prophylactic value in patients admitted to hospital with postinfluenzal pneumonia who are not infected with *Staph aureus* on admission but who are liable to become superinfected with antibiotic-resistant hospital strains of *Staph aureus*

It would be interesting to know whether the patients in whom postinfluenzal staphylococcal pneumonia developed were, in normal circumstances, nasal carriers of the organism, and whether the lung infection was derived from the strains present in the nose If this were so, the 30–40% of the community at large who are nasal carriers of *Staph aureus* would be at a special risk during influenzal epidemics

Summary

During the influenza epidemic in the autumn of 1957 140 patients with pneumonia were admitted to this hospital

Among the 38 patients infected with *Staph aureus* the mortality was noticeably greater (47%) than in the remainder (16%)

There was evidence that 13 of the 140 patients were infected in hospital with strains of *Staph aureus* which were resistant to penicillin, aureomycin, streptomycin, and sulphonamides

We wish to thank the physicians of the City General Hospital under whose care the patients were admitted, Dr A J N Warrack for the necropsy findings, Dr J E M Whitehead for the virological investigations, Dr E H Gillespie for the results of staphylococcal phage-typing, and Dr E H Gillespie and Dr J Beasley for advice and criticism

REFERENCES

French H (1920) *Rep publ Hlth med Subj , Lond*

Gould J C Cruikshank J D (1957) *Lancet*, ii, 1157

Stuart Harris, C H (1953) Influenza and Other Virus Infections of the Respiratory Tract London

METASTATIC PANOPHTHALMITIS FOLLOWING COMMONPLACE SURGICAL INFECTIONS

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PANOPHTHALMITIS is an acute purulent infection involving all the coats of the eye and usually follows a perforating wound, whether this be operative or accidental. A further means of infection is by metastatic spread from some other focus, in these cases the panophthalmitis may present either as part of a general septicæmia or as an isolated lesion, and the true nature of an inflamed and painful eye may often remain obscure until irreversible damage has been done to delicate intraocular structures. If, however, panophthalmitis is recognised early, the sight of the affected eye may be saved.

Two cases are reported here not only because of the difficulty in diagnosis but also because of the rarity of panophthalmitis now that antibiotics are used more widely in early cases of general and ocular infection.

Case-reports

CASE 1.—A housewife, aged 28, reported to hospital on Feb. 17, 1957, with two weeks' history of a tender swelling of her left breast. She had previously always been well. Twenty-five days earlier she had given birth to twins and had been given stilbœstrol tablets immediately afterwards to suppress lactation. On the tenth day post partum she had in her left breast a painful swelling which was diagnosed by her doctor as an incipient breast abscess and treated with penicillin injections for a week. This produced marked symptomatic improvement, and she then applied kaolin poultices for a further week, during which time her symptoms recurred.

On examination she looked ill and had an obvious large breast abscess beginning to point vertically above the nipple. No other abnormality was found. Under general anæsthesia the abscess was incised, and about 8 oz. of thick yellow pus was evacuated from a multilocular cavity occupying the greater part of the breast. The loculi were broken down, and the cavity was drained.

Postoperative course.—On the fourth postoperative day the patient complained of watering and irritation of her right eye. Examination showed mild conjunctival injection but little else. She was treated with sulphacetamide-sodium ('Albucid') eyedrops for presumed conjunctivitis. Next day the irritation had changed to pain, her vision had become blurred, and she had ciliary injection and chemosis. Acute iritis was diagnosed and treatment begun with atropine eyedrops and hot bathing. On the sixth day hydrocortisone eyedrops were prescribed in addition to the atropine. The pain and chemosis, however, gradually increased, and on the seventh day a rise in tension of the globe was noticed. This, with the increased pain, was thought to be due to secondary glaucoma, and acetazolamide ('Diamox') tablets 500 mg. initially, followed by 250 mg. four times daily, were given. By the ninth day the pain had become very severe and throbbing and radiated to the frontal region, teeth, and nose. Chemosis was gross, as was œdema of the lids, and vision was restricted to appreciation of bright light. At this stage panophthalmitis was suspected, and a retrobulbar injection of crystalline penicillin 1,000,000 units with 2% lignocaine 0·5 ml. and hyaluronidase 1 ml. was given. Hot bathing was continued, streptomycin 0·5 g. was injected intramuscularly twice daily, and the patient was heavily sedated.

Operation.—The patient's condition having remained unchanged, on the twelfth day, under general anæsthesia, the sclera was incised at the level of the pars plana of the ciliary body. Thick pale-yellow pus was liberated. Exploration of the orbit revealed no further pus. The cornea was then incised, and pus was irrigated from the anterior chamber. Complete seclusio pupillæ was found.

Postoperative course.—Next day the patient's condition was greatly improved, the œdema, pain, and chemosis all gradually settled, and two weeks later she was discharged with a slightly painful and blind eye. During the following six months the eye became painless and then shrunken. Her breast healed normally, and at no time was there evidence of any other metastatic lesion. Her temperature was raised on admission but fell after the incision of the breast abscess. It did not rise above 99°F until the ninth postoperative day, when the panophthalmitis was fully established.

Laboratory investigations.—From both the breast and the eye similar organisms were cultured, namely coagulase-positive staphylococci sensitive to streptomycin, terramycin, and chloramphenicol but resistant to penicillin.

CASE 2.—A diabetic woman, aged 46, attended hospital on Sept. 11, 1956, with a paronychia of her left index finger. She had this incised as an outpatient under local anæsthesia, and a small amount of pus was released. She was not given any antibiotics. A few days later she felt unwell and became pyrexial. On the advice of her doctor she rested in bed, but the malaise continued and she developed polydypsia and polyuria and became nauseated. On Sept. 23, 1956, she had noticed bilateral deterioration of vision, accompanied by pain in her left eye which radiated to the frontal region.

On admission to hospital on Sept. 25, 1956, her temperature was 100°F and she had glycosuria and acetonuria. Her eyelids on both sides were œdematous, there was bilateral ciliary injection, and both pupils were unresponsive to light. A cloudiness was visible in both anterior chambers, and vision was restricted in the left eye to appreciation of light and dark only, and in the right eye to appreciation of coarse hand movements.

Diagnosis, treatment, and course.—Bilateral iritis with secondary glaucoma and uncontrolled diabetes was diagnosed, and treatment with cortisone and atropine eyedrops, and with insulin was instituted. On Sept. 28, 1956, her temperature had become normal although her eyes had improved only a little. On this day a trace of albumin and some pus cells were found in her urine, and on abdominal palpation a soft spleen tip was felt. Urine and blood cultures were made, and the true nature of the ocular condition was now recognised as probably a metastatic panophthalmitis secondary to septicæmia. Treatment with crystalline penicillin 8,000,000 units daily, streptomycin 2 g. daily, and chloramphenicol 2 g. daily was begun. By Oct. 2, 1956, although the right eye was slowly improving, the left eye had lost all vision and was painful and proptosed, and there was considerable periorbital œdema.

Operation.—On Oct. 3, 1956, under general anæsthesia, the left eye was explored, found to contain a large amount of pus, and eviscerated.

Postoperative progress.—This was satisfactory, the antibiotics being discontinued on Oct. 14, 1956. The gradual improvement of the right eye was maintained, which progress was hastened by two five-day courses of corticotrophin in the next six weeks, the first course being covered by a further week's course of chloramphenicol 2 g. daily and terramycin 2 g. daily. When the patient was discharged on Dec. 3, 1956, she had been stabilised (after some early difficulty) on insulin zinc suspension 56 units daily, her left eye had healed satisfactorily, and her right eye, in which the vitreous was still clearing, had a visual acuity of 1·5/60.

Follow-up.—A year later, in November, 1957, her visual acuity was 6/60, and some scarring was visible above the macula, this presumably being the site of the original choroidal or retinal abscess. Again in this patient, in spite of septicæmia, there was no high pyrexia. At no time did her temperature rise above 101°F which was recorded only on one occasion.

Laboratory investigations.—Unfortunately the pus from the infected finger was not cultured. The blood-sugar levels on Sept. 26, 1956, were 235 mg. per 100 ml. in the morning and 255 mg. per 100 ml. in the evening. On Sept. 28, 1956, cultures of blood and urine (catheter specimens) both grew *Staphylococcus aureus* slightly sensitive to penicillin and sensitive to chloramphenicol, streptomycin, and terramycin, and the number of white blood-cells was 8900 per c mm (polymorphs 84%, lymphocytes 14%, monocytes 2%) On Oct 2, 1956, three days after the start of antibiotic therapy, a blood-culture again yielded staphylococci On Oct 16, 1956, and thereafter blood-cultures proved negative

Discussion

Metastatic infection of the eye was first recognised by Virchow (1856) and Axenfeld (1894) published a series of such cases Most of the cases recorded since occurred in pre-antibiotic days, when loss of the affected eye was almost inevitable Donahue (1943), however, reported a recovery from panophthalmitis in a man, aged 52, who developed the infection a week after perurethral prostatectomy and was successfully treated with sulphadiazine Today, with prompt antibiotic treatment (promptness is the important factor), it may be possible to save the vision of the affected eye in a large proportion of cases

The primary lesions in published cases have ranged from otitis media and pneumonia to furunculosis (Spicer 1907), and the most usual infecting organisms have been streptococci, staphylococci, and (less commonly) coliform bacilli The presence of frank septicæmia (as in case 2) is by no means an invariable accompaniment of metastatic panophthalmitis, but septicæmia was probably the cause of death in many of the earlier published cases

Typically panophthalmitis is of dramatic onset, but it was not so in these two patients Again, the temperature is commonly considerably raised, but in these two cases pyrexia was not prominent in the clinical picture The usual presenting symptoms are pain in the eye, malaise, headache, and drowsiness, and the signs are those of conjunctival and ciliary injection, œdema of the lids, and chemosis and a hazy appearance of the cornea The iris appears "muddy", and the posterior corneal surface becomes covered with precipitates A vitreous haze develops, and eventually this haze increases until, on retinoscopy, all view is obscured and the yellow reflex is obtained These signs may develop in a few hours or take several days to become manifest Eventually the pain becomes very severe, the intraocular tension rises considerably, and the eye becomes fixed and proptosed The differential diagnosis is from an intraorbital, as opposed to an intraocular, abscess

The earlier that treatment is begun the better because, once suppuration has started, the delicate intraocular structures become irreversibly damaged (Duke-Elder 1940, 1954), and, even if the eye is saved, the end-result, so far as visual acuity is concerned, may be disappointing With the first symptom or sign, treatment with atropine eyedrops and local heat, which may be applied by bathing or by short-wave diathermy, should be instituted Cortisone locally and either corticotrophin or cortisone systemically should be tried The antibiotic to be given will depend on the sensitivity of the organism, which may be assumed if the organisms of the original lesion have been cultured as in case 1 If the organism is not known, a conjunctival swab should be taken and treatment started with local and systemic penicillin Locally penicillin may be administered by subconjunctival or retrobulbar injection It is probably wise, owing to the common occurrence of penicillin-resistant infections, to combine this with some other antibiotic therapy Penicillin given systemically does not pass the blood-aqueous barrier, hence the need for local and systemic administration, although sulphonamides do pass this barrier Of the other antibiotics the most satisfactory, after experimental and clinical trials, appears to be chloramphenicol in a dosage of up to 6 g daily (Leopold et al 1950) This may also, with advantage, be applied locally as drops or ointment Terramycin appears to be relatively unsatisfactory (Sorbsy et al 1953) If a combination of antibiotics are given at any one time, it should be remembered that they do not always exert a synergistic effect Streptomycin may also be given by subconjunctival injection, and the intraocular levels obtained are higher if adrenaline is added to the injection

Sorsby and Ungar (1958) have favourably reported on the use of neomycin in intraocular infections Neomycin is a true broad-spectrum antibiotic and thus is effective against the organisms likely to be the cause of panophthalmitis Although clinical experience of its use is limited, for subconjunctival injection neomycin 0 5 g dissolved in 0 75 ml of water to which 0 25 ml of 1 1,000 adrenaline has been added is recommended Neomycin is toxic, so probably not more than 2 g should be administered by this route Again, another antibiotic should be given systemically in metastatic panophthalmitis

If the condition is recognised only at a late stage or does not respond to vigorous antibiotic therapy, resort will have to be made to surgery Usually evisceration is the operation of choice because enucleation involves the danger of spread of the infection to the subarachnoid space round the optic nerve, leading to meningitis

It is interesting to note that the incidence of intraocular metastatic carcinoma is very low, even in patients with widespread carcinomatosis, about 70% of those which do occur are said to be secondary to breast carcinoma (Cohen 1937)

In both cases reported here acute iritis was diagnosed in the early stages In case 2 the true nature of the process was recognised with the development of signs of septicæmia, and prompt antibiotic treatment saved the second eye Although coincident but quite divorced ocular conditions are undoubtedly more common in such patients, any person presenting with an acutely inflamed eye and a recent history of pyogenic infection should be suspected of having metastatic panophthalmitis, especially if the tension of the globe is raised

Summary

Two cases of metastatic panophthalmitis, one following drainage of a breast abscess and one, which was bilateral, following a paronychia, are described

The infrequency of metastatic panophthalmitis and the importance of early antibiotic therapy, both local and systemic, if vision is to be saved, are noted

Any patient with an acute iritis and a recent history of pyogenic infection should be suspected of having metastatic panophthalmitis

I wish to thank Mr K W Wilkinson and Mr J S Phillpotts for help in preparing this paper and permission to publish case 1, and Dr J R Nassim for permission to publish case 2

REFERENCES

Axenfeld, K T P P (1894) v *Graefes Arch Ophthal* 40, 1
Cohen, M (1937) *Arch Ophthal N Y* 18, 604
Donahue, H C (1943) *Amer J Ophthal* 26, 283
Duke-Elder W S D (1940) Textbook of Ophthalmology, vol III London.
— (1954) *ibid* vol VI London
Leopold I H, Nichols, A, Vogel, A W (1950) *Arch Ophthal, N Y* 44, 22
Sorsby, A, Ungar, J (1958) *Ann R Coll Surg Engl* 22, 107
— — Crick R P (1953) *Brit med J* ii 301
Virchow, R (1856) *Virchows Arch* 9, 307
Spicer, W T H (1907) *Trans ophthal Soc U K* 27, 230

TOTAL CARDIOPULMONARY BYPASS IN THE LABORATORY

A PRELIMINARY TO OPEN HEART SURGERY

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Early in 1957 we began work on total cardiopulmonary bypass, hoping that within a year we could employ a heart-lung machine on patients requiring deliberate open cardiac surgery This limited aim has been achieved, and the techniques learnt in the laboratory have been translated to the operating-theatre Lillehei et al (1956) and Kirklin et al (1956) in the U S A had developed satisfactory bypass techniques well before we started, the most superficial study of their work reveals the stress they placed on painstaking laboratory preparation We outline here the work done by a team anxious to gain the knowledge necessary to carry out safe total cardiopulmonary bypass

The Apparatus

We use a Lillehei-deWall pump-oxygenator (deWall et al. 1957) (fig 1) The pump, a 'Sigmamotor T-6S',* has identical arterial and venous heads in which a length of latex tube is compressed against a spring-loaded back-plate by each of a series of twelve steel fingers in turn milking the blood along The speed of action, and thus the delivery-rate of each head is independently variable Blood passes from the caval cannulæ to the venous pump (In the last 11 perfusions we have used a gravity drainage venous well [deWall et al 1958]) From the pump the blood passes up a vertical tube, the oxygenator, into which oxygen is bubbled through a perforated disc at its lower end During this ascent the blood is oxygenated and then passes down into a wider tube, the debubbler, set at 25° to the horizontal and coated with a silicone antifoam (I C I M430 †) to break the bubbles, it flows from the debubbler into a long spiral tube, the helix, immersed in a thermostatically controlled water bath at a temperature of 41°C In the helix any remaining bubbles rise, so that blood leaving the base of the helix is bubble-free. The helix also acts as a reservoir in which the volume of blood can be accurately observed The arterial pump takes blood from the helix and passes it to the arterial cannula through a simple monofilament nylon-mesh filter, which also serves as an additional bubble trap

Apart from the latex in the pump heads all the tubing is of transparent polyvinyl chloride ‡ The various connections, including the perforated plate for introducing the oxygen, are made of highly polished stainless steel or nylon All apparatus in contact with blood is sterilised by autoclaving in sealed nylon tubular foil bags § Although providing a barrier to bacterial contamination, these bags are permeable to steam during autoclaving and allow subsequent drying

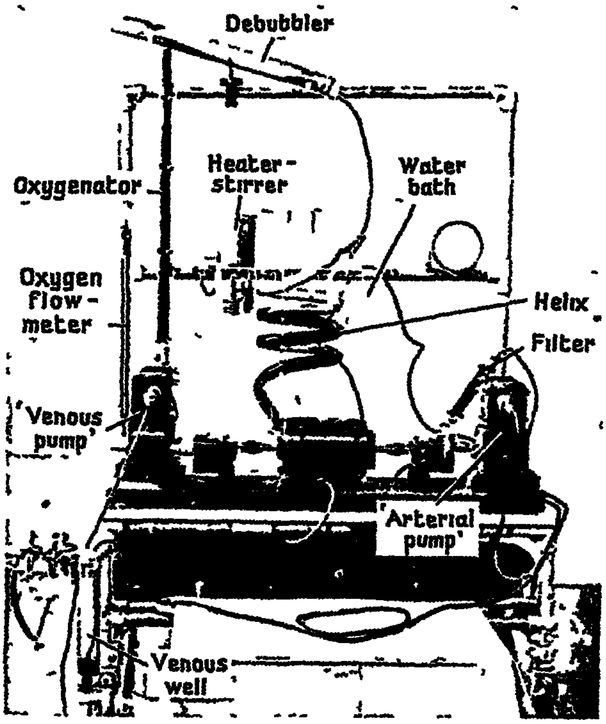

Fig 1—Lillehei-deWall heart-lung machine, with arterial and venous hoses connected.

Preliminary Studies

Before animal work was started, many hours were spent in handling the machine so that we became familiar with its behaviour It was found that, with correct adjustment of the back-plates, the pump output was independent of inflow pressures from −50 to +50 mm Hg and of outflow pressures up to 400 mm Hg

Oxygenation was studied using fresh heparinised venous ox-blood It was found that a ratio of oxygen to blood-flow of 5 1 by volume ensured 98% oxygenation at rates of flow between 500 and 800 ml per min of 24% oxygenated venous blood

Mechanical hæmolysis was also studied Plasma-hæmoglobin levels were less than 150 mg per 100 ml after continuous circulation of ox blood, equivalent to perfusion at 900 ml per min for one hour These experiments also showed that debubbling was satisfactory

Monitoring (fig 2)

A monitoring technique has been established to give continuous records of the aortic and inferior vena caval pressures, electrocardiogram (E C G), electroencephalogram (E E G), and œsophageal temperature (fig 2)

The recording apparatus is an Ediswan four-channel pen oscillograph The manometers used for measuring the pressures are of a valve transducer (R C A 5734) type modified from a design by Arnott et al (1951) Calibration is effected by connecting each manometer through three-way taps to a system filled with heparinised isotonic dextrose incorporating a pressure bottle and a valve ¶ as a precaution against air embolism This obviates the use of long fluid columns and thus gives a rapid and accurate method of repeated calibration.

The E C G electrodes are safety-pins inserted subcutaneously in each shoulder and the left leg The E E G electrodes are two tempered-steel pins varnished except for the tips lightly hammered into the frontal and occipital regions of the skull of the anæsthetised dog in the parasaggital plane An optional earth electrode is similarly sited in the midline over the frontal sinus A cut-out device connected with the diathermy foot pedal protects the E C G and E E G recorders when the diathermy is in use

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[2] Of the Department of Physiology

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† Imperial Chemical Industries Ltd , Nobel Division, 25, Bothwell Street, Glasgow, C.1

‡ Capon Heaton Ltd , Hazelwell Mills, Stirchley, Birmingham

§ Portex Plastics Ltd , Bassett House, Hythe, Kent

¶ The 'Oxford Safety Dropper' (Macintosh and Pask 1941), Medical and Industrial Equipment, 10–12, New Cavendish Street, London, W 1

No biochemical monitoring has been performed

Preliminary Animal Studies

None of the team had had previous experience of dog surgery or anæsthesia The monitoring apparatus was therefore set up on three dogs under anæsthesia and blood was collected for hæmolysis experiments In two of these dogs cadaver perfusions were performed in order to gain experience in making the necessary incisions and carrying out the cannulations No other acute experiments were done

Procedure

Every experiment was conducted under the same conditions as those in the operating-theatre The dogs used were unselected mongrels weighing 7 5–17 5 kg Large dogs were used as donors to provide blood to charge the machine No dog was obviously ill, and no preoperative treatment was given Preoperative hæmoglobin estimations and cross-matching of donor and recipient dogs were performed Agglutination was occasionally seen, incompatibility was then assumed, and the donor dog changed

Donor blood is collected by slow bleeding of the anæsthetised dog (vide infra) after cannulation of the carotid artery and external jugular vein Before bleeding, heparin 2 mg per kg of body-weight is given intravenously and the blood is collected into 500 ml bottles containing 9 mg heparin in isotonic dextrose solution The donor dog is killed Meanwhile the machine is assembled, using aseptic technique, and calibrated with physiological saline solution to give the desired flow-rate (this was originally 60 ml per kg body-weight per min , but recently has been increased to 80 ml per kg per min and above, giving total flows up to 1500 ml per min) The saline solution is then drained from the venous side of the machine and from the arterial side, leaving two inches in the helix and the arterial hose and filter full (280 ml) The machine is charged with 800–1000 ml of donor blood This provides a helix content during perfusion equivalent to approximately half a minute's flow (This is only half the amount in the helix recommended by Lillehei [deWall et al 1958] Though we were aware of this, we wished to economise on donor dogs Using the machine with this small charge provided a more stringent test of the efficiency of the helix and also gave less latitude for errors in handling the machine) The arterial and venous hoses are connected to each other, the pumps are started, and the blood is circulated The hoses are inspected until all bubbles have been removed from the arterial side

Anæsthesia

Anæsthesia is induced in the unpremedicated dog with thiopentone 10 mg per kg body-weight and succinylcholine chloride 1 mg per kg body-weight intravenously The dog is intubated and anæsthesia is maintained with nitrous oxide and oxygen in a semiclosed circuit incorporating a Waters' canister Increments of up to a quarter of the induction dose of barbiturate or relaxant are given as required Atropine 0 66 mg (gr $^1/_{100}$) is given intravenously at the time of induction and repeated later if excessive salivation occurs

The Surgical Approach

The dog is placed on a heated operating-table and the operation fields are prepared by clipping, shaving, and washing the skin The E C G and E E G electrodes and the œsophageal thermometer lead are inserted, and the diathermy earth electrode is applied Benethamine penicillin 600,000 units and streptomycin 0 5 g are given intramuscularly An intravenous drip through a Guest cannula is set up in the cephalic vein The clotting-time of the venous blood is done by the Dale and Laidlaw (1911) method 1 mm nylon cannulæ for the manometers are inserted into the abdominal aorta and inferior vena cava through the femoral vessels

A longitudinal incision is made in the neck for access to the left common carotid artery A right fourth interspace thoracotomy is made to expose the heart and the great vessels (In the last eight perfusions a bilateral transternal thoracotomy has been carried out, allowing left brachial instead of carotid cannulation) Before the vessels are cannulated heparin 2 mg per kg is given intravenously Thin rubber tubes are passed around the superior and inferior venæ cavæ at their junction with the right atrium to act as tourniquets The arterial cannula is of the design described by Drew et al (1957), but the rigid parts are of nylon In only two dogs have we failed to insert an arterial cannula at least 3 8 mm in internal diameter The venous cannulæ, which are simple vinyl tubes, have never been of a smaller internal diameter than 4 mm and are usually 6 mm (For the first thirty experiments they were passed into the venæ cavæ through separate auricular incisions, but now a single incision is made in the auricular appendage and the

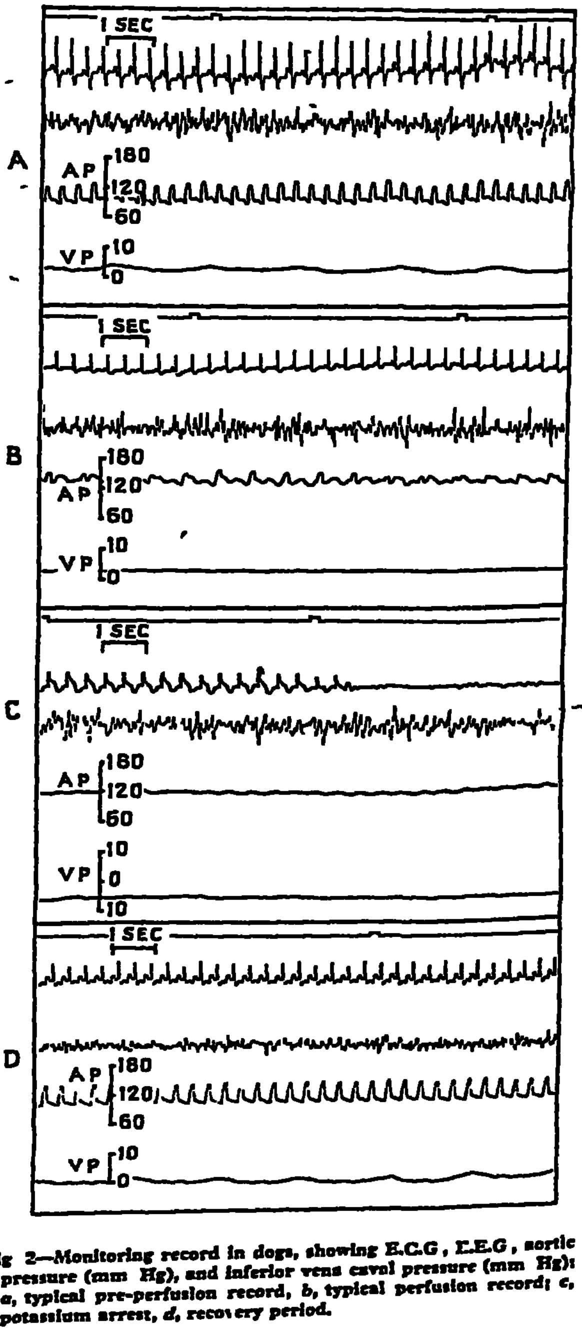

Fig 2—Monitoring record in dogs, showing E.C.G , E.E.G , aortic pressure (mm Hg), and inferior vena caval pressure (mm Hg): *a*, typical pre-perfusion record, *b*, typical perfusion record; *c*, potassium arrest, *d*, recovery period.

cannulæ are passed through two holes bored in a sponge-rubber grummet inserted in this incision.)

During the whole of the operation meticulous hæmostasis is maintained, the total blood-loss, including that due to cannulation, is rarely as much as 30 ml. before perfusion, measured by swab-weighing.

The Perfusion

Immediately before connecting the hoses to the cannulæ the blood is circulated for a minute and the hoses are again inspected for the presence of bubbles on the arterial side. A bubble-free junction is then made between the arterial hose and the arterial cannula. The venous hose is joined to the two venous cannulæ by means of a stainless-steel Y tube, small bubbles being of no moment. Perfusion is begun by starting the machine, unclamping the hoses, and tightening the caval tourniquets. The animal is then on total cardiac bypass. We have never failed to achieve satisfactory perfusion as evidenced by adequate arterial-perfusion pressure (80/60 to 140/100 mm. Hg), and a satisfactory grade of E.E.G. (Hudson 1958) (fig. 2). The main task of the pump operator during perfusion is to maintain a constant volume in the helix. If perfusion is unsatisfactory, it is corrected on information from the monitor and from the pump operator.

On sixteen occasions simple perfusion varying in duration from 10 to 75 minutes has been performed. In the remaining experiments, satisfactory perfusion having been established, a further procedure has been carried out. In six perfusions the heart has been arrested with potassium citrate and in the remaining twenty a right ventriculotomy has been performed, sixteen of these on the potassium-arrested heart (see accompanying table and fig. 3).

Potassium Arrest

The first five potassium arrests (Melrose et al. 1955) were done by aortic injection, but this resulted in such troublesome bleeding from the puncture that all subsequent arrests were done by injection into the left ventricle. None of the twenty-two hearts arrested with potassium has failed to restart and ultimately to maintain effective circulation with a normal arterial pressure. The period of recovery, however, has been as long as 25 minutes, and has been punctuated by episodes of atrioventricular dissociation, ventricular asystole, ventricular tachycardia, and ventricular fibrillation. Ventricular asystole and bradycardia due to heart-block occurring after the heart is closed cause distension of the heart due to coronary-sinus return, and on these occasions an artificial pacemaker (Lightwood 1958a) has been used to stimulate the heart to eject its contents. Ventricular fibrillation has been stopped by an electrical defibrillator, employing a 300-volt D.C. shock of 1/50 second duration (Lightwood 1958b). Cardiac bypass has always been maintained until sinus rhythm has been re-established and effective left ventricular ejection observed on the aortic pressure tracing.

Perfusion is ended by releasing the caval tourniquets, stopping the pump, and simultaneously clamping the arterial and venous hoses. The arterial and venous cannulæ are removed, the artery and the right auricular appendage are ligated and transfixed.

Closure

Protamine sulphate 0.5% is given very slowly intravenously until a total of 2 mg. protamine for each mg. heparin used has been given. The clotting-time is then repeated and increments of protamine 0.25 mg. per mg. heparin are given if necessary until the clotting-time is within 20 seconds of its original value. We think this is preferable to protamine titration (Perkins et al. 1956), which is slow and complicated. We have had no difficulty in restoring the clotting-time to normal and

DATA ON PERFUSION EXPERIMENTS IN DOGS

Experiment no.	Duration of perfusion (min.)	Flow-rate		Procedure	"Walking time"	Survival-time (days)	Causes of death
		Total (ml. per (min.)	ml. per kg per min.				
1	10	600	63	P	4 hr	Kd, 14	
2	15	500	42	P	1 day	Kd, 17	
3	30	550	60	P		1	Hole in superior vena cava, hæmothorax, collapse of rt. lung
4	30	697	56	P	1 day	Kd, 5	Symptoms of distemper, at necropsy, pneumonia
5	45	455	38	K	4 hr	Kd, 15	
6	36	484	51	P		2 hr	Spontaneous respiration but never conscious, at necropsy, gross fatty liver
7	12	550	42	P		4 hr	Accidental overtransfusion
8	30	600	47	P	6 hr	Kd, 15	
9	45	550	58	P	3 hr	Kd, 17	
10	45	560	56	K	12 hr	4	Anæmic postoperatively, transfused, 'paraplegic' after 2 days, at necropsy, bilateral cerebral infarcts
11	30	600	60	K	2 hr	Kd, 16	
12	45	750	61	P	2 hr	Kd, 15	
13	45	860	61	K	20 hr	2	Comatose 2nd day, at necropsy, cerebral œdema
14	41	900	60	K and V	1½ hr	Kd, 18	
15	46	370	41	V	1 day	Kd, 14	
16	45	600	70	P		8 hr	Hæmothorax, overtransfused with citrated blood, at necropsy, gross venous congestion
17	45	500	67	V	3 hr	Kd., 14	
18	33	667	55	K and V		12 hr	Overtransfused, at necropsy, aneurysm of right ventricle and gross venous congestion
19	43	750	58	K and V		8 hr	Overtransfused, at necropsy, gross venous congestion
20	35	500	43	K and V		2 hr	Overtransfused, at necropsy, gross venous congestion
21	30	666	63	P	4 hr	Kd, 15	
22	40	750	70	V	4 hr	Kd, 21	
23	50	540	65	V	15 min	Kd, 21	
24	21	700	64	P		12 hr	Paraplegic, but conscious, perfusion death
25	36	700	56	K	1½ hr	Kd, 21	
26	28	700	63	P	30 min	3	Hypotensive during operation, at necropsy, bronchopneumonia
27	65	600	66	K and V	2 hr	Kd 15	
28	38	750	65	K and V	1½ hr	8	Wound dehiscence, bilateral pneumothorax
29	21	600	67	P	1 hr	8	Wound dehiscence, empyema, death during surgical decortication
30	30	855	75	P	1 hr	Kd, 14	
31	30	780	60	K	5 hr	Kd., 14	
32	31	850	74	K and V	2 hr	Kd, 17	
33	39	850	77	P	12 min	Kd., 15	
34	76	800	76	K and V	2 hr	Kd., 14	
35	25	850	81	K and V		4 hr	Neurological signs of cerebral damage
36	24	880	70	K and V	20 min	Kd., 14	
37	49	930	85	K and V	9 hr	Kd, 14	
38	41	1020	85	K and V	1 hr	Kd, 14	
39	43	750	94	K and V		8 hr	Helix emptied during perfusion, neurological signs of cerebral damage
40	55	850	95	K and V	8 hr	Kd., 14	
41	45	1250	66	K and V	1 day	Kd, 14	
42	32	1500	97	K and V	2 days	Kd, 9	

P = simple perfusion. K = perfusion and elective potassium arrest. V = perfusion and right ventriculotomy.
'Walking-time' = time from insertion of last stitch to walking. Kd = killed on or after 14th postoperative day (excluding dog 42, killed at 9 days).

saturated fatty acids in high concentration may be consumed without raising cholesterol levels above the "basal value" for the individual * Our experience indicates that the basal values are about 30% below the levels ordinarily found in Western society Perhaps modification of foodstuffs may enable us to achieve the blood-cholesterol levels now seen in populations which have low morbidity and mortality from atherosclerosis

We are indebted to Dr A T James, of the National Institute for Medical Research, Mill Hill, for the analytical data One of us (L H) receives a grant from the National Research Council, Canada

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SERUM-CHOLESTEROL LEVELS AFTER CONSUMING EGGS WITH INCREASED CONTENT OF UNSATURATED LIPIDS

The rise in serum-cholesterol level which follows consumption of hens' eggs is something of an enigma It is not due to their cholesterol or protein content,[1] [2] and it is generally attributed to a fatty-acid factor Egg-yolk lipids, however, are only moderately saturated (iodine value 70–80)[3], and their cholesterogenic effect is greater than would be expected on the "degree of saturation" hypothesis of Ahrens et al[4] Furthermore, egg-yolk lipids contain about 20% of linoleic acid[5] (in addition to 32% of saturated fatty acids, 47% of oleic acid, and 2% of linolenic acid) and thus their cholesterogenic effect cannot readily be explained in terms of the essential-fatty-acid deficiency postulated by Sinclair[6] and by Kinsell et al[7]

While considering this we recalled an old report by Cruickshank,[5] who found that when hens were fed on a diet rich in hempseed, the linoleic-acid content of their yolk lipids rapidly rose from 19 to 44%, with a corresponding fall in saturated and oleic acids, at the same time, the iodine value of the yolk lipids rose from 80 to 120 Accordingly, in the hope of shedding some light on their cholesterogenic mechanism, we decided to compare the effects of ordinary and "unsaturated" hens' eggs on the human serum-cholesterol level

A flock of Black Australorp hens was chosen for our experiments During an initial 2-week control period they had a stock diet containing 3% of fat with an iodine value of 93 Eggs were collected on four occasions, and the iodine value of their yolk lipids averaged 72 (S D 1) Half the hens were then placed in a separate henhouse and were given a special feed which included sunflower seeds (80% dehulled) The other half continued with their ordinary diet The composition of the control and the experimental feeds is shown in the table

Percentage composition of the hen feeds

	Control feed	*Experimental feed*
Mealie meal	59·0	31·0
Bran	11 0	4 3
Lucerne meal	11 0	8 7
Peanut-oil cake	5 0	
Fish meal	6 5	3·5
Limestone powder	2 0	3 5
'Fermavite' (molasses fermentation product)	1·0	2 5
'Premix' (commercial bone-meal and salt mixture)	4 5	3 5
Sunflower seeds (80% dehulled)		43 0
Percentage fat contents (by analysis)	3·0	15 0

From now on four eggs were gathered from each hen house weekly The yolk lipids from the hens on the experimental feed showed a progressive increase in iodine value, and by the end of 3 weeks this had reached 100, at which level it remained for the duration of the experiment The iodine value of the yolk lipids from the control hens did not change and at 3 weeks averaged 73 (standard deviation 1 5) At this stage all the eggs from the control and the experimental hens were collected and used for human feeding trials The experimental egg yolks were a deeper yellow than the controls, but when they were cooked they could not be distinguished by taste

The experimental hens throve on their diet, and their egg-production was in no way inferior to that of the controls It interested us to find that, after the 6 weeks, the mean serum-cholesterol level of the ten experimental hens was 117 mg per 100 ml (S D 23), compared with 166 mg (S D 34) these mean values were significantly different (P less than 0 02) By this time the body fats of the experimental hens had become relatively unsaturated the values for the control and experimental hens respectively were abdominal fat, 76 and 94, subcutaneous fat, 76 and 85, muscle fat, 77 and 91, liver fat, 77 and 90 Too few analyses were performed, however, to permit of any statistical comparison

The effect of feeding these eggs was studied in 2 healthy Bantu male volunteers, each 34 years old During the experiments they lived in the metabolism ward and received the basal diet, very low in fat (11 g daily), which we have previously described[2] Except as indicated below, their diets were kept constant with respect to calories (2500 daily) and protein (88 g daily)

Experiment 1 (fig 1)—On the basal diet, the mean serum-cholesterol level was 75 mg per 100 ml Introduction of ten boiled "control" egg-whites into the daily diet for 10 days did not alter it When they were replaced by ten boiled control egg yolks daily for 10 days, it rose to 100 mg These were then replaced by ten boiled "unsaturated" yolks, and during the next 10 days the serum-cholesterol level fell to 95 mg per 100 ml —a trivial change In the next period, ten whole "unsaturated" eggs fried in 100 g of sunflower-seed

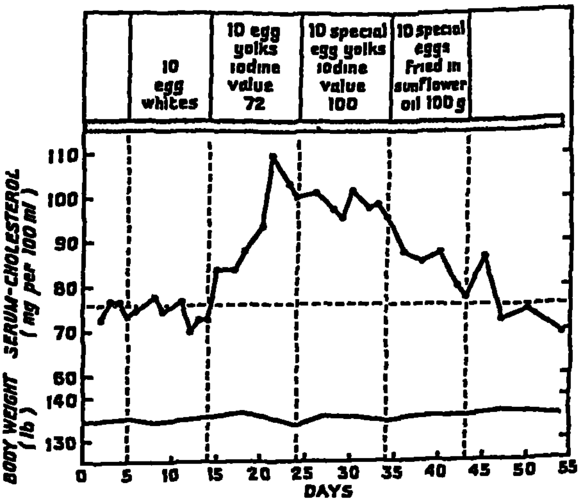

Fig 1

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* Since this communication was first submitted, two more subjects have been tested The ingestion of ten eggs daily (high in unsaturated fatty acids) resulted in a gradual return of the serum-cholesterol levels from low-fat basal levels to control levels in a 2-week test period With stock eggs, the serum-cholesterol rose more abruptly and reached higher levels

1 Messinger, W J, Prosowska, Y, Steele, J M *Arch intern Med* 1950, 86, 189
2 Bronte-Stewart, B, Antonis, A, Eales, L, Brock, J F *Lancet*, 1956, i, 521
3 Deuel, H J, Jr The Lipids Their Chemistry and Biochemistry, vol 2 London, 1951
4 Ahrens, E H, Jr, Hirsch, J, Insull, W, Tsaltas, T T, Blomstrand, R., Peterson, M L *Lancet*, 1957, i, 943
5 Cruickshank, E M *Biochem J* 1934, 28, 965
6 Sinclair, H M *Lancet*, 1956, i, 381
7 Kinsell, L W, Michaels, G D, Friskey, R W, Splitter, S *ibid* 1958, i, 334

oil were eaten daily (3100 calories, 112 g. protein), and by the 9th day the serum-cholesterol level fell to 77 mg.—i.e., practically to basal level. On returning the subject to his basal diet there was a temporary rise in the serum-cholesterol, but it quickly returned to the basal level.

In this first experiment there was no difference in the effect on the serum-cholesterol level of "control" and "unsaturated" eggs. It remained possible, however, that if the latter had been eaten for more than 10 days the cholesterogenic effect of the control eggs might have been reversed. In the next experiment, therefore, the unsaturated eggs were fed without a preliminary period on control eggs.

Experiment 2 (fig. 2).—During an initial 6-day basal period, the serum-cholesterol level averaged 188 mg. per 100 ml. Then ten boiled unsaturated egg yolks daily were introduced into the diet and fed for 7 days; the serum-cholesterol level promptly rose to 218 mg. The subject was then returned to his basal diet and 3 g. of cholesterol daily (i.e., the amount in ten yolks) was mixed with his food for the remaining 8 days of the experiment. The serum-cholesterol quickly returned to the basal level, and this showed again that the serum-cholesterol-increasing action of eggs is not due to their cholesterol content.

It appears from these two experiments that increase of the iodine value of egg yolks from 72 to 100 does not materially affect their cholesterogenic action. Although egg-yolk lipids with iodine value of 100 markedly raise the serum-cholesterol level, we have frequently observed that certain other more saturated fats, such as hydrogenated sunflower seed oil (iodine value 74), do not raise the serum-cholesterol, and that some, such as olive oil (iodine value 88) and peanut oil (iodine value 89), sometimes lower it. Thus we conclude that the effect of all dietary fats on the serum-cholesterol level is not simply a function of their degree of saturation.

The suggestion of Keys et al.[8]—that, to offset the cholesterogenic effect of saturated fatty acids, at least twice as much polyethenoid fatty acid is required—might appear to be a satisfactory explanation of our findings; thus, the additional linoleic acid introduced into the unsaturated eggs may not have sufficed to neutralise their saturated-fatty-acid content. In Cruickshank's experiments,[3] the polyethenoid-fatty-acid content of her unsaturated eggs was more than double their saturated-fatty-acid content; had we been able to "unsaturate" our eggs beyond iodine value 100, it is conceivable that we might have produced a "cholesterol-decreasing" egg. It must be noted, however, that in several other dietary experiments in man, a fall in serum-cholesterol has been produced with far less than a 2 : 1 ratio of polyethenoid to saturated fatty acids. For example, fig. 8 of our paper last December,[9] shows that the cholesterogenic effect of 100 g. of hydrogenated coconut oil (almost all saturated fatty acids) was abolished by 100 g. of sunflower-seed oil—i.e., by only 65 g. of linoleic acid. In a number of long-term studies of active men consuming their ordinary diets, which were often rich in saturated fats, we found that by simply administering 50 g. of sunflower-seed oil (about 33 g. of linoleic acid) daily, a substantial decrease in the serum-cholesterol level was usually produced and maintained.[10] It may be that the rule of Keys et al.[8] is valid when applied to their type of "group" experiment but we agree with Kinsell[11] that the *individual* response to a dietary fat is variable and cannot be predicted by a mathematical formula.

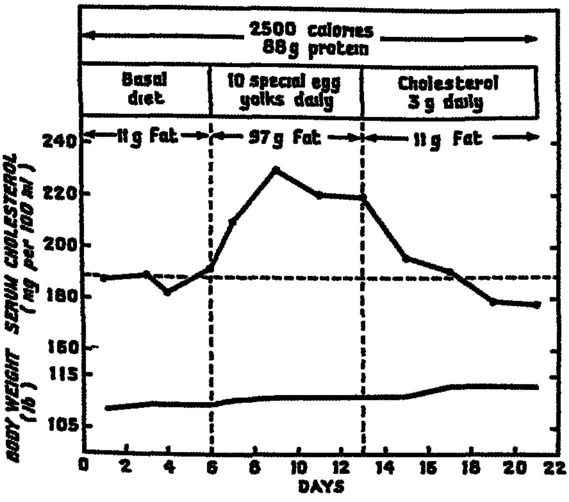

Fig 2

We have no data on the individual fatty-acid components of our control and unsaturated egg yolks, but on the basis of Cruickshank's findings[3] we have assumed that the unsaturation of the latter is achieved by an increase in the proportion of linoleic acid at the expense of the monoethenoid and saturated fatty acids. Failure of this presumed rise in the linoleic-acid content of our eggs to inhibit the cholesterogenic effect seems to be at variance with the "essential fatty acid deficiency" hypothesis. We must point out, however, that it is not known whether the "linoleic acid" of egg yolks is the biologically active *cis-cis* isomer or not. It is known that the "linoleic acid" of a number of animal fats is in the inactive form,[12] isomerisation apparently having taken place in the process of digestion, absorption, or deposition of the active linoleic acid of the diet. Thus, Hilditch and Longenecker[13] found that, despite an abundance of natural linoleic acid in pasture grasses, the depot fats of ruminants contain very little of it; most of the octadecadienoic acids of these fats are in the *trans-cis* or other isomeric forms. It is possible that the failure of our unsaturated egg yolks to decrease the serum-cholesterol level is due to isomerisation of the linoleic acid of the dietary sunflower seeds in the course of its incorporation into the egg yolk.

The above speculation implies acceptance of the "essential fatty acid deficiency" hypothesis. This hypothesis, however, is far from proven: hypercholesterolæmia does not occur in animals fed on a diet deficient in essential fatty acids,[14] nor is there any direct evidence of such deficiency in hypercholesterolæmic human beings. It is true that Kinsell et al.[7] have shown that 95% pure linoleic acid can lower the serum-cholesterol level of man, but the effect of its "non-essential" isomers has not been studied. We must conclude that the factor or factors in dietary fats which regulate the serum-cholesterol level are still unknown.

These experiments were performed with the cooperation of Dr M. Finlayson, the owner, and Mr J. Mirvish, the manager, of the farm Kelvin Grove in the Constantia valley. We are grateful to them for their kindness.

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8. Keys, A., Anderson, J. T., Grande, F. *ibid.* p. 742.
9. Gordon, H., Lewis, B., Eales, L., Brock, J. F. *ibid.* 1957, ii, 1299.
10. Gordon, H., Brock, J. F. *S. Afr. med. J.* 1958, 32, 397.
11. Kinsell, L. W. *Lancet*, 1958, i, 857.
12. Hilditch, T. P. Chemical Constitution of Natural Fats. London, 1956.
13. Hilditch, T. P., Longenecker, H. E. *Biochem. J.* 1937, 31, 1805.
14. Deuel, H. J., jr., Alfin-Slater, R. B., Wells, A. F., Kryder, G. D., Aftergood, L. *J. Nutr.* 1955, 55, 337.

Reviews of Books

Clinical Biochemical Methods

A L TÁRNOKY, B SC, PH D, biochemist, Royal Berkshire Hospital, Reading London Hilger & Watts 1958 Pp 239 50s

MOST departments of clinical biochemistry or chemical pathology have a "methods book", which contains, usually in alphabetical order, descriptions of the techniques used in the department These are concise résumés but leave out no essential detail The junior technicians use this collection of recipes rather as a young housewife would her cookery book, and the more senior members of the laboratory refer to it for a quick refresher To be entered in such a laboratory book is high praise for a technique because it implies that it has been tested by the worker on the bench, found reliable and worthy of becoming a part of his everyday routine There is a tendency to adhere to one particular method once it has been accepted and not to bother about minor or sometimes even major improvements the accent is on reliability and convenience rather than on striving to be entirely up to date Dr Tárnoky's book is such a one, describing "the biochemical analyses in routine use in the laboratory of the Royal Berkshire Hospital"

Most methods required in clinical biochemistry are here assembled, but the natural history of such a summary of techniques explains why the choice is somewhat uneven Thus the method for estimating serum-calcium is the old-fashioned precipitation of the calcium as oxalate and the subsequent titration of the oxalate by permanganate On the other hand, serum-chloride is determined by the swift titration with mercuric nitrate with diphenylcarbazone as the indicator Serum electrophoresis for separating protein fractions is described, but no mention is made of the determination of urinary amino-acids and sugars by chromatography, or of the instantaneous identification of glucose in urine by the use of test papers or sticks containing glucose oxidase The urine tests are somewhat neglected Sulkowitch's test for calcium and Bial's test for pentoses (though the osazone test is mentioned) might have been included No test for fructose in urine is given It might be questioned whether anyone can describe satisfactorily the determination of the basal metabolic rate, of alkali reserve, of serum-protein fractions by electrophoresis within a few pages each Yet as far as he can go Dr Tárnoky has produced here masterpieces of concise clarity This book will be particularly useful in hospital laboratories which do not include a biochemical department and where a morbid anatomist must take responsibility for the reliable biochemical investigation of hospital patients

A History of Public Health

GEORGE ROSEN, M D, PH D, M P H, professor of health education, School of Public Health and Administrative Medicine, Columbia University New York M D Publications 1958 Pp 551 $5 75

THE history of public health is the story of man's endeavours to protect himself and his community against disease and of the attitudes of society towards the sick throughout history In primitive communities, down to the Middle Ages, society's defence against sickness, physical or mental, was to isolate or destroy the patient, later came the endeavour to heal the sick and so prevent them from infecting or harming their fellow men or becoming a burden on society, and finally the establishment of positive protection of the healthy from the dangers of disease

Professor Rosen has long been recognised as one of the world's foremost medical historians and an acknowledged leader in matters of public health Here, in the first of a new series of monographs on medical history, his pen has skilfully traced the procession of men, deeds, and facts that have taken a vital part in the story of public health, and the tremendous tasks that had to be faced

As late as 1808 the inhabitants of Exeter emptied their sewage in the gutters, and in the entire town there was only one water-closet The introduction of this amenity, however, soon created more problems than it solved, since the cesspits were cleaned out very rarely and the contents seeped into the soil, saturating the ground over large areas and polluting springs and wells It was deceptively easy to dispose of sewage by allowing it to discharge into the sewers that existed under many cities by this time, but they were solely designed to carry off rainwater, and so, as the practice became more general rivers and lakes in or near all the larger towns were turned into open sewers This was to be one of the major problems facing the sanitary reformers of the nineteenth century

The book is well documented and contains an appendix of short biographies

Heart Disease and Pregnancy

Physiology and Management C SIDNEY BURWELL, M D, Samuel A Levine professor of medicine, Harvard University, JAMES METCALFE, M D, associate in medicine, Harvard University Boston Little, Brown & Co London J & A Churchill 1958 Pp 338 72s

THIS work is based on the authors' experiences in the Boston Lying-In Hospital It begins with a brief historical survey showing the dramatic fall in maternal mortality from heart-disease in the hospital between 1921 and 1927, and a further decline in 1937–39 There follows a full account, well illustrated by graphs, of the physiological maternal changes in pregnancy Other chapters deal with the incidence of heart-disease among pregnant women, diagnostic criteria for heart-disease, prognosis, maternal and fœtal mortality, and the management of the pregnant patient with heart-disease, with special reference to the indications for termination of pregnancy A chapter is devoted to rheumatic fever in pregnancy, and the remainder of the book covers the problems of pregnancy in different forms of congenital and acquired heart-disease Particular attention has been paid to mitral stenosis and the question of valvotomy in pregnancy The concluding chapters cover less common types of heart-disease and neurocirculatory asthenia This book will undoubtedly prove of great value to physicians, obstetricians, and cardiologists, its great merit being the emphasis on the extensive personal experience of the authors

Hypnography

AINSLIE MEARES, M B, D P M Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 271 58s 6d

DR MEARES has for some years done pioneer work in the field of hypno-analysis, and this clinical study, well written and thoughtfully presented, will interest any psychotherapist aware of the value of hypnosis A description of the preliminaries to hypnosis, the methods of inducing hypnosis, and the technique for hypnography itself leads to an account of the kind of material produced The patient, hypnotised while sitting at a desk, is given a brush and black paint and it is suggested that he shall paint whatever is in his mind The drawings thus produced are illustrated in a series of over 200 figures, and their dynamic content discussed, both in general terms and specifically in excerpts from case-histories The book might have been less expensive if some of the figures had not been duplicated

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A Short History of the Order of St John (London St John Ambulance Brigade Headquarters 1958 Pp 83 2s 6d)—The black and white uniforms of the St John Ambulance Brigade are a familiar sight at all our public functions But few realise that the men and women who wear them are lineal descendants of the knights of one of the oldest known orders of chivalry And many members of the Brigade would themselves find it hard to say how long ago the Order was founded, or how its present functions have evolved This booklet by Mr E D Renwick sets out in easy and attractive style a story which begins in the twelfth century in Amalfi, a small republic south of Naples, and which continues to the present day, for the eight-pointed white cross, once the badge of that republic, is still the emblem of the Order of St John The account is freely illustrated All those doctors who have been associated with the Brigade would do well to read it, they may well feel, after its perusal, that their stature has increased

THE LANCET

LONDON 2 AUGUST 1958

Another Renal Symposium

IN medical literature the post-war scene (as we hopefully call it) has been dominated by the multiple-author textbook and the conference report This multiplication of opinion between the same covers reflects progress in the application of several disciplines and habits of mind to a single group of problems, rather than an escape from monolithic authority into a confusion of experimental facts, and as such it is to be welcomed, even though it may make for bitty reading The kidney has been well served by such publications, including in this country the Ciba symposium in 1953,[1] the Cushny memorial lectures,[2] and the issue of the *British Medical Bulletin* on renal physiology and pathology[3] An important series of "seminars" on renal physiology appeared in the *American Journal of Medicine* in 1950, and now, following the changing fashion in nomenclature, we have in the same journal a "symposium on renal function"[4]—though it may be doubted whether the first series of papers was delivered to small discussion groups, or the second at a drinking-party The renal outsider may perhaps wonder what new thing can be said on this theme, but he has only to look into this most recent symposium to discover, with the active nephrophile,[5] that these are exciting times in which our knowledge of that marvellous organ, the kidney, is being added to in many ways

In their preface, G H MUDGE and J V TAGGART, the editors, draw attention to four "areas" in which "considerable progress is apparent" These are "the morphology and cellular fine structure of the nephron, concepts in the clinical appraisal of renal disorders, descriptive electrolyte physiology, and the cellular mechanisms which operate in renal tubular transport" Each of these "areas" seems to us perhaps to represent part of a larger whole, which might be summarised as a shift of emphasis towards tubular function and away from glomerular function and renal plasma-flow It is scarcely possible to overestimate the contribution made to renal physiology and pathology by the clearance techniques of HOMER SMITH, but there was a period about a decade ago when a superficial observer might have thought that the kidneys were of importance mainly in excreting substances such as inulin and *p*-aminohippurate (P A H), which they never normally encounter, rather than in regulating the output of physiological constituents of the urine To be sure, the limits of action of change in glomerular filtration-rate (G F R) on urine formation had to be defined, and it cannot be denied even now that fall in G F R is a major factor both in "extrarenal uræmia" and in some types of generalised œdema, but the attempt to make changes in G F R responsible for any alteration in salt balance has failed This failure is currently recognised in the term "glomerular-tubular imbalance", which is perhaps best regarded as an unhappy symbol of a transition period in applied renal physiology Progress is now coming from the application of new techniques and new thinking to the very varied functions of the renal tubule As examples of this we may mention the detailed study of the processes by which the urine is made acid, stemming from the work of PITTS and his colleagues[6], the application of DENT's technique of paper chromatography to define the "clinical patterns of tubular dysfunction", now reviewed by MUDGE[7], the use of histochemistry[8] and of nephron dissection[9] in localising functional and structural lesions of the tubule, and of course the description of the effects of aldosterone and other hormones on the tubular handling of electrolytes

New approaches to tubule function are well represented in the latest symposium PITTS[10] reviews the information on the site of action of various diuretics which is being obtained in his department by the "stop-flow" method—an ingenious technique in which the urine flow in dogs is arrested for a few minutes, after which continuous frequent samples are taken from the ureter At high rates of urine flow, stimulated by mannitol, successive samples of urine differ in composition in a way suggesting that they represent the fluid in successive segments of the nephron up to and including Bowman's space Analysis of twenty to thirty such samples in each experiment gives results consistent with a distal-tubule site of action of acetazolamide, but with a predominantly proximal-tubule action of the mercurial diuretic chlormerodrin MILNE and his colleagues[11] describe how differential permeability of membranes leads to a concentration of weak bases in acidic fluids and of weak acids in alkaline fluids, this concept is important not only in relation to ammonium excretion but also in the pharmacology of important agents such as salicylate, mecamylamine, and pempidine[12] Dilution and concentration of the urine, so often taken for granted or used as an empirical test of renal failure, are now reviewed in worthy detail by BERLINER et al,[13] who propose a modification of the ingenious but somewhat neglected "counter-current" physical mechanism of WIRZ[14] Some new thinking is certainly needed here to account for such apparent anomalies as the failure of water diuresis in hypopituitarism,[15] the inability of healthy people to form a concentrated urine for some days after a period of water-loading,[16] and the formation of a concentrated urine in the absence of antidiuretic hormone when G F R is reduced [17] TAGGART [18] reviews progress in the very difficult problem of active tubular transport Much of this progress has been negative, in the elimination of " mechanisms proposed in the past on rather superficial grounds ", but his account of glucose reabsorption and of P A H secretion indicates at least the way in which the application of metabolic energy to active transport is likely to be elucidated

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[1] The Kidney (edited by A A G Lewis and G E W Wolstenholme) London 1954

[2] Winton, F R. Modern Views on the Secretion of Urine London, 1956

[3] *Brit med Bull* 1957, 13, no 1

[4] *Amer J Med* 1958, 24 659

[5] Platt, R *Brit med J* 1952, i, 1372

[6] Pitts, R F, Alexander, R S *Amer J Physiol* 1945, 144, 239

[7] Mudge, G H *Amer J Med* 1958, 24, 785

[8] Pearse, A G E, Macpherson, C R *J Path Bact* 1958, 75, 69

[9] Oliver, J, MacDowell, M, Welt, L G, Holliday, M A, Hollander, W, Winters, R W, Williams, T F, Segar, W E *J exp Med* 1957, 106, 503

[10] Pitts, R F *Amer J Med* 1958, 24, 745

[11] Milne, M D, Scribner, B H., Crawford, M A *ibid* p 709

[12] Harrington, M, Kincaid-Smith, P, Milne, M D *Lancet*, July 5, 1958, p 6

[13] Berliner, R W, Levinsky, N G, Davidson, D G, Eden, M *Amer J Med* 1958, 24 730

[14] Wirz, H, Hargitay, B, Kuhn, W *Helv physiol pharmacol acta*, 1951, 9 196 Wirz, H Proceedings of the 8th Symposium of the Colston Research Society London, 1957

[15] Oleesky, S, Stanbury, S W *Lancet*, 1951, ii, 664

[16] de Wardener, H E Communication to Medical Research Society 1957 Epstein, F H, Kleeman, C.R. Hendrikx, A *J clin Invest* 1957, 38, 629

In addition to the emphasis on tubular function, the papers in this symposium illustrate another way in which renal physiology is drifting away from the dominance of clearance techniques The first two papers, on electron microscopy [19] and on renal biopsy,[20] reflect the renewed interest in structure as a necessary basis for function These two papers are a partial fulfilment of some of the hopes expressed by JEAN OLIVER in his contribution to the 1950 series, entitled " an essay toward a dynamic morphology of the mammalian nephron " [21] Perhaps fortuitously, another paper in the present series, by BRADLEY and WHEELER,[22] stresses the differences between nephrons, in contrast to their statistical unity which is the unstated assumption of the clearance approach—an assumption which was pilloried by OLIVER in the trenchant query "When is a kidney not a kidney?" [23] So far from being uniform, the nephrons are apparently " notably multifarious, in dimensions, mass, configuration, construction and arrangement ", the evidence of a functional counterpart to these obvious variations in structure is still indirect, but it is increasing in cogency, even for the normal kidney

Looking at the symposium in general, it is apparent that the questions are still well ahead of the answers, but at least they are different questions, and perhaps in the long run more easily answered Most of the advances reported have been in physiology, and have not yet been digested into practical clinical use, but the work on diuretics,[10] on renal biopsy,[20] and on the kidney in potassium depletion [24] is already at this stage Most of the territory, in which we have planted a few signposts, lies between the desert and the sown, and it is not yet certain whether some of the concepts expressed will turn out to be words (" the daughters of earth ") or things—" the sons of Heaven " in the round Johnsonian phrase

The Right Background

THE part that physical environment plays in the treatment of physical illness has long been appreciated fresh air, sunshine, particular kinds of food, and exercise —all are recognised as often therapeutic Today we are beginning to appreciate the equal importance of mental environment in the treatment of mental illness, and this rediscovery is helping to change the atmosphere of mental hospitals In the past, as Dr DUNCAN MACMILLAN pointed out last week,[1] the environment of these places has too often not even been neutral it has been actively unhelpful Certification, deprivation of civil rights, segregation from the rest of the community, and confinement behind locked doors are procedures which, however well intentioned, can only increase the tension, uncertainty, and bewilderment of the patient and aggravate the disturbance of his mind and feelings

But environment can do more than fail to hinder recovery It can actively speed the patient's progress, and today the hospital environment is no longer regarded as a mere custodial background—against which active therapy flamed and then too often faded—but as part of the patient's treatment The clearer this becomes, the more important it is that he should be placed in the most suitable environment, and this in turn demands a subtler classification of patients according to their needs and a greater diversity of hospital accommodation Unlike many reforms, this may prove an economy as well as an advance Professor MCKEOWN and his colleagues [2] in their survey of 3555 residents in Birmingham mental hospitals found that only 13% needed the full range of hospital facilities, 75% needed only limited hospital services, and 12% needed none of the traditional ones MCKEOWN thinks that in the hospitals of the future these three different kinds of patients should be in separate units

Ways in which the hospital unit can be varied according to the patient's need have also been discussed by Dr MINSKI, drawing on his experience as physician and superintendent of a neurosis centre from 1938 to 1957 [3] In his view the ideal administrative framework for the care of mental patients would comprise a neurosis hospital, an acute psychiatric hospital, and a hospital for long-stay patients—all under the same management committee, and with the same senior doctors working in all three In this way the task of looking after the chronic cases would be shared between the medical staff He suggested that registrars coming fresh from general medicine should begin their psychiatry in the neurosis centre, where they would find patients of a kind already familiar to them He would like to see some beds in general hospitals reserved for neurotic and psychosomatic cases so that medical and nursing staff should have more experience of looking after these patients Observation wards should also, in his view, be attached to general rather than mental hospitals, for many of the patients admitted to these beds would then never need to go to a mental hospital But if in this way the general hospital could usefully take part in the care of the mental patient it should in return have help in its outpatient department To give the necessary continuity of care, a psychiatrist from the complementary mental hospital should be on the staff of the outpatient department of the general hospital

Dr MINSKI has described his ideal, albeit an ideal formed by experience Dr BAKER on p 253 describes a reality in which progress, if not perfection, is being achieved by improvisation Like Professor MCKEOWN and Dr MINSKI, he asks for the division of our huge monolithic mental hospitals into smaller, livelier, friendlier units, and he describes how, at Banstead Hospital, a modest start has already been made A non-statutory unit and a tuberculous unit have already been opened, and in defiance of structural difficulties the 1200-bed institution is to be divided up and transformed, if all goes well, into three admission hospitals, a geriatric hospital, a hostel, and a reablement unit Dr BAKER believes that if we made better use of our hospital beds we should not need so many of them The Banstead experiment in functional division is a brave effort to free psychiatric practice from the domination of what he justly describes as our "huge over-populated unwieldy mental hospitals"

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[17] Berliner, R W, Davidson D G *J clin Invest* 1957, 36, 1416
[18] Taggart J V *Amer J Med* 1958 24, 774
[19] Rhodin J *ibid* p 661
[20] Brun C, Raaschou F *ibid* p 676
[21] Oliver J *ibid* 1950 9, 88
[22] Bradley S E, Wheeler H O *ibid* 1958, 24, 692
[23] Oliver J *J Urol* 1950, 63 373
[24] Relman, A S Schwartz, W B *Amer J Med* 1958, 24, 764

[1] Macmillan D *Lancet* July 26 1958, p 201
[2] Garratt, F N, Lowe, C R, McKeown, T *ibid* 1958, i 682
[3] Minski, L, in a paper read to the Royal Medico-Psychological Association on Feb 22 1958

Annotations

TREATMENT OF THE PSYCHOPATH

SOME of the most obstinate problems in psychiatry revolve round the clinical condition known as "psychopathic personality" The very concept is so hard to delimit and so open to argument that the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency, while advocating wide compulsory powers, left the definition open[1] But the diagnosis is child's play compared with the difficulties of management, and the remarks on treatment by Dr Melitta Schmideberg, chairman of the Association for the Psychiatric Treatment of Offenders, in a lecture to the Institute for the Study and Treatment of Delinquency on July 23 were of great interest

Drawing on her experience in Europe and the United States, Dr Schmideberg pointed out that the usual criterion of psychopathy was antisocial behaviour, but this did not necessarily involve breaking the law The narcissistic element was pronounced, and this love of self with slight regard for others led to a peculiar idea of reality in which the future consequences of present actions could not be judged the capacity to learn from experience was similarly one-sided, and, while the psychopath's errors seemed to make him more adept in criminality, punishment was not often deterrent Ideas of grandeur and "magical" modes of thinking seemed to be involved in his usual belief that he could not be caught Although the whole life-pattern showed self-destructive tendencies, suicide among psychopaths was rare the borderline between psychopathy and schizophrenia was sometimes vague and could be crossed in either direction There was always a strong wish for pleasure, and a need for immediate gratification, but the capacity for enjoyment was slight Although anxiety and guilt were said to be characteristically absent, Dr Schmideberg was sure that they existed but were denied indeed antisocial acts often arose as an expression of anxiety The sadistic element was clear enough in the various aggressive acts, and, as Dr Peter Scott pointed out in the discussion, masochistic traits in some cases made punishment worse than useless since this was just what the patient unconsciously sought

As to the origins of the condition, Dr Schmideberg, for a psychoanalyst, laid surprisingly little emphasis on trauma in early life Maternal deprivation was but one factor She pointed out that increasing numbers of psychopaths in America come from well-ordered middle-class homes, similarly there were deprived slum children in whom psychopathic traits did not develop The development of social ideals and self-control was what socialised, and it was in this area that the psychopath was most disturbed The prevalence of crime was greatest not in towns like New York and Chicago but in affluent areas such as California She felt that American ideals were becoming increasingly psychopathic, crime bred crime, and vivid newspaper reporting had much to answer for (It could be added to her list of external causes that tough police methods constitute a "challenge" to delinquents which may have much to do with the extreme violence of some American adolescent outbursts)

Dr Schmideberg believed that treatment out of prison was often preferable, since only in society could the patient face his relationship problems in the work and sexual sphere The difficulty was that the severe psychopath did not *want* to change his sole interest in doctors was in using them to get out of trouble For this reason interpretations of behaviour given during psychotherapy would probably be used by the patient as an excuse for further offences and a means of putting the blame for his behaviour on to others (e g, his parents) Analytic treatment must be employed with caution, and the defences against real insight were enormous Success could be hoped for in reluctant patients only when they were obliged under threat of punishment to receive treatment, thus probation and suspended sentences were, in Dr Schmideberg's view, invaluable Some doctors disliked the idea of their patients being "forced" to receive treatment from them, but it was the unwilling ones who required attention most urgently The art of the therapist consists in turning the enforced relationship into a genuine one, and it was mainly this genuine relationship that socialised the patient Under the suspended sentence, the sentence was postponed and finally pronounced after periodic appearances in court and reports from the therapist This and probation, she considered, were admirable devices, which provided just the right blending of authority with threat from the court and support from the therapist The initial relationship came most easily just before the trial, and she used challenging and directive methods related to real-life situations concerning the patient's actions and their consequences The process of producing motivation was half the problem, and, once the patient wished to change, the process became one of re-education One criterion of success was stability at work, for if a man was not in work he would steal Adjustment was always hard, because the psychopath expected disproportionate praise for anything he did Dr Schmideberg departed again from analytic practice in that she verified incidents and progress by means of information from the family, employer, and probation officer if it could be tactfully obtained without hurting the patient

Dr Maxwell Jones rightly indicated in the discussion that relationships in the work and sexual spheres could be built up in certain kinds of institution, and that commentary and prohibition might be more effective to the patient when derived from his peers instead of from authority Many will differ from Dr Schmideberg's views and methods, but their particular virtues seem to be their realism and common sense It is to people with her energy and positive approach that we look for new ideas and methods—the trouble is that methods already in use remain somewhat unknown quantities Apart from the work at Belmont,[2] Simpson has an interesting unit at Wormwood Scrubs,[3] and elsewhere different types of formal psychotherapy and psychoanalysis have been used Everyone working in or observing these endeavours must agree that "things happen" (treating psychopaths may be trying but it is certainly not uneventful), and the dynamic situations that arise are of much scientific interest But the ultimate results are hard to judge, and comparison of one kind of management with another is impossible

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[1] Royal Commission on the Law Relating to Mental Illness and Mental Deficiency, 1954-57, paras 190-195, 357 H M Stationery Office, 1957

WHY PEOPLE SMOKE

TEMPERAMENTAL differences between smokers and non-smokers have been described by Heath[4], and now McArthur et al[5] have published further observations on the same group of men Their subjects were 252 Harvard graduates who, while at the university in 1938–42, were selected for a study of adult development because of their apparent normality They were examined by psychological and various other techniques, and their progress was checked by annual questionaries, tests, and visits Smoking habits were among the extensive data collected about these men, and information accumulated over a fifteen-year period was available for analysis

Believing with Bales[6] that the social and cultural environment is the most potent influence on habit formation, McArthur et al considered that non-smoking was likely to be commonest in the lower middle class of the U S A , since there is evidence[7 8] that people of this rank, more than those above or below them in the social scale, still cleave to values derived from what has been called the Protestant Ethic[9]—religious doctrine according to which it is sinful to waste time and substance on unprofitable activities Children reared in this tradition are taught to eschew frivolity, and to be upright, industrious, and ambitious[8 10 11] It seemed probable, therefore, that members of the middle class would be less likely to indulge in a pleasure of the flesh, such as smoking, than members of other less ascetic sections of the population In order to test this hypothesis they compared the smoking habits of men who had prepared for Harvard at public high schools with those of men who had prepared for Harvard at private preparatory schools, as the high-school graduates were mainly of middle-class and the preparatory-school graduates of upper-class origin They found, in fact, that there was a highly significant correlation between smoking and exclusiveness of school 20% of the graduates of very exclusive private schools, 30% of the graduates of less exclusive private schools, and 40% of the graduates of public schools did not smoke At first sight it might appear that a public-school education is less conducive to smoking than a private-school one, but this is not so, *for it has been estimated*[12] that only 9% of boys at American public schools do not smoke! It must therefore have been *from this select minority* that the Harvard public-school non-smokers were recruited They were predominantly earnest young men of the middle class, the pride of their families, heavily indoctrinated with "work morality", and bent on achieving the status of a technical or professional career The upper-class private-school boys, on the other hand, aimed rather at conformity with an accepted code of behaviour than at advancement through self-denial, and most of them went into business A significantly high proportion of non-smokers had pious parents, and the sons were often more pious than the fathers In short, it would appear from the findings of this investigation that a comparatively poor but very honest Protestant, keen to "improve himself", is more likely than most in America to remain a non-smoker, and McArthur et al quote a market survey carried out in England[13] which suggests that here also non-smoking is associated with "middle class respectability"

Whatever the reason for starting to smoke, it may be assumed that the degree of addiction will be determined by the extent to which the habit satisfies the personal needs of the smoker It is generally believed that smoking is indulged in to allay anxiety, but McArthur et al found no convincing evidence of a general tendency in their subjects to smoke more heavily in times of stress, *although they admit that their experiment was not ideally* designed to test this point However, as 70% of heavy smokers and only 30% of light smokers said they smoked more when under pressure, it seemed possible that smoking may become a suitable tension reducer only when it has become a deeply ingrained habit Heavy smoking in their study was found to be most significantly correlated with a "coartated" performance of a special Rorschach test—that is, a record indicative of a lack of emotional resources Coartated men were "inarticulate, pragmatic, and bland hard to get to know compulsive fiddlers, desk-arrangers, people who allayed their tension through fussy activities" Once a coartated person started to smoke he tended to smoke heavily, no matter what his social background had been Moreover, he tended to smoke increasingly, so that if he started late he was soon smoking more than men who had started early Among the heavy smokers who were not coartated there was, as Heath[4] has already observed, a significantly high proportion of impulsive men with poorly integrated personalities

As regards ability to stop smoking, the amount of tobacco previously consumed was found to be the most *significant factor* It was estimated that men who have smoked a mean number of 9 cigarettes a day can stop, men who have smoked 18 do not try, and men who have smoked 20 cannot (Presumably it is assumed that some 18-a-day men can stop if they try) The ability of the subjects of the study to stop smoking was also significantly related to the length of time they had been breast-fed Light smokers who could stop had been weaned at 8 months, heavy smokers who could stop had been weaned at 6 8 months, smokers, mostly heavy, who did not try to stop had been weaned at 5 months, and smokers, mostly heavy, who tried to stop but could not had been weaned at 4 7 months McArthur et al do not suggest that there is an immediate connection between early weaning and inability to stop smoking—the time of weaning may reflect only a certain pattern of infant training—but they point out that smoking is associated with a liking for other oral gratifications. smokers tend to drink more alcohol and coffee than non-smokers,[4] and if they stop smoking they are apt to substitute food for tobacco.[14] Also, a lower than average proportion of men who could stop smoking had been bottle-fed babies, and a higher than average proportion of men who could not were reported to have sucked their thumbs in childhood. McArthur et al. therefore conclude that, although the amount of tobacco previously consumed is of prime importance in determining whether or not a person can stop smoking, an "orality" factor may also be influential.

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[2] Jones, M , et al Social Psychiatry Tavistock Publ London, 1952

[3] Landers, J J , McPhail, D S , Simpson, R C *J ment Sci* 1954, 100, 953

[4] Heath, C W *Arch intern Med* 1958, 101, 377 See *Lancet*, 1958, i 680

[5] McArthur, C , Waldron, E , Dickinson, J *J abnorm soc Psychol* 1958, 56, 267

[6] Bales, R F *Quart J Stud Alcohol* 1946, 6, 480

[7] McArthur, C *Harvard educ Rev* 1954, 24 256

[8] McArthur, C *J abnorm soc Psychol* 1955, 50, 247

[9] Weber, M The Protestant Ethic (Translated by Talcott Parsons) New York, 1930

[10] McClelland, D , Rindlisbacher, A , De Charms, R Studies in Motivation, p 389 New York, 1955

[11] Miller, D C , Form, W H Industrial Sociology New York, 1951

[12] Hollingshead, A Elmtown's Youth New York, 1949

[13] Davis, F Unpublished

Perhaps the most interesting finding of this study is that in the past some parents, on general principles, have persuaded their children not to smoke. Now that the perils of cigarette smoking are so widely known, it would be even more interesting to learn what parents are managing to persuade their children to avoid the habit on the specific ground that it is dangerous to life.

ANTIBODY TO PENICILLIN

Ley *et al.*[15] have reported a new and interesting observation—that specific antibody to penicillin may be demonstrated in some human sera. The discovery was made accidentally. Penicillin was added as a routine to preserve red-cell suspensions used in a blood bank. The serum of one prospective recipient of a transfusion was found to agglutinate all red cells against which it was tested, but the agglutination did not appear when the same serum was tested against red cells which had not been mixed with penicillin. When the patient's red cells were treated with penicillin, they also were agglutinated by his own serum. Investigation showed that red cells of all human blood-groups could be made agglutinable to antibody-containing sera in this way, but so far only with the penicillins G, O, and K, and the penicillin derivative synnematin B. Results were negative in tests with streptomycin, dihydrostreptomycin, polymyxin B, bacitracin, neomycin B, ristocetin, viomycin, and oleandomycin, but it is not stated whether cells sensitised with these agents were put against sera likely to contain antibody to them or only against sera known to contain antibody to penicillin. Penicillin inactivated by penicillinase did not sensitise the red cells, but red cells once sensitised could not be desensitised by subsequent treatment with penicillinase, papain, or ficin. Sensitisation of red cells with penicillin proceeded in proportion to the concentration of the drug and time of exposure, reaching a maximum in about twenty-four hours and persisting for as long as the cells remained useful for testing—that is, for some two to three weeks.

To carry out tests for serum antibody, Ley et al. prepared penicillinised red cells by adding 8 ml. of a mixture of equal parts of whole blood and Alsever's solution to 200,000 units of powdered penicillin G. After incubation at 37°C for an hour the red cells were washed thrice in physiological saline solution and made up to a suitable suspension (4–10%) in physiological saline. The incubation temperature was not critical, since sensitisation could be accomplished at any point in the range 6–37°C. Antibody was eluted from sensitised cells by heating them at 54°C for fifteen minutes, the antibody was stable at refrigerator temperatures and resisted 56°C for two hours. Its possession of many of the known attributes of a true antibody, and its specificity, thus appear to be well established; further, it may be completely adsorbed from sera by their exposure to concentrations of penicillin of the order of 12,000 units per ml. or greater. A positive reaction between antibody-containing serum and sensitised red cells may be easily demonstrated by conventional slide or tube agglutination methods if there is enough antibody, and by anti-globulin methods if there is not. So far, Ley et al. have detected 25 positive sera among about 2000 tested. All who yielded positively reacting sera had received penicillin treatment at some time, but only a minority had been known on clinical grounds to be sensitive to penicillin.

This report is of great interest both because it offers a possible method of studying the sensitisation of patients to penicillin—an important problem in its own right—and because, despite the negative results with other antibiotics so far tested, this report raises the hope that the valuable method of red-cell agglutination may perhaps, with appropriate technique, be yet found adaptable to the study of other hypersensitivity phenomena, which cause so much distress to their victims and appear to be an increasing feature of medical practice.

EXPERIMENTAL MONILIASIS

MONILIASIS is attracting attention because overgrowth of the causal agent, *Candida* (formerly *Monilia*) *albicans*, is commonly observed in patients treated with antibiotics—particularly, it seems, with broad-spectrum antibiotics such as chloramphenicol and the tetracyclines. Usually this overgrowth is without clinical significance, but exceptions are common enough to maintain our interest in the influences that may favour or counteract invasion of tissue by *C. albicans*. Studies of these problems are reviewed by O'Grady and Thompson,[1] who describe their own experimental approach, which has novel and notable features.

To begin with, they chose to work with a lesion produced by inoculating *C. albicans* into the left thigh of mice. This was done to eliminate the uncontrollable and unmeasurable effects that might arise in experiments where a local bacterial flora was normally present. It is suspected that, in actual practice, monilial overgrowth may be due partly to suppression of normal flora, but the unresolved question which was studied was whether an antibiotic might have a more direct effect either on the growth of the candida or on the defences of the host. The closed lesion in the thigh of the mouse met this point. Furthermore, objective, accurate, rapid, and frequent measurements of the progress of the experimental infection could be made by measuring daily with sliding callipers the mediolateral diameters of the thighs and thence calculating the average increase compared with the normal thigh. O'Grady and Thompson examined Seligmann's[2] postulate that chlortetracycline (aureomycin) exerts on the response of the host to candida infection an effect analogous to that of cortisone. In the effects of cortisone and chlortetracycline they discovered, by their approach, two similarities and two differences. Both drugs caused a decrease in size of the experimental lesions, which was followed by a rapid increase when treatment was stopped. In addition, if the dose of chlortetracycline was high enough, the diameter of the thigh on the side

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14. Brozek, J, Keys, A *Science*, 1957, 125, 1203
15. Ley, A B, Harris, J P, Brinkley, M., Liles, B, Jack, J A, Cahan, A. *ibid*, 1958, 127, 1118.

1. O Grady, F, Thompson, R E M *Brit J Pharmacol* 1958 13 1
2. Seligmann, E *Proc Soc exp Biol*, N Y 1952, 79, 481 1953, 83, 778

of the lesion continued to be above the control value, as with cortisone—a demonstration of the rebound effect, already well known with cortisone

Intramuscular injection of cortisone alone reduced the diameter of the thigh a little, and injection of cortisone along with candida reduced the candida lesion compared with untreated controls Chlortetracycline by itself, on the other hand, produced a large swelling, and if given along with candida produced a very large and persistent mass When the drugs were given subcutaneously to animals which received the candida separately, the suppression and rebound resulting from cortisone could not be reproduced by subcutaneously administered chlortetracycline in any dosage On the contrary, the reduction in size of the lesion from subcutaneously administered chlortetracycline became increasingly long-continued with increased dosage, but rebound was not observed even when the chlortetracycline was given for two days only From other experiments, which involved the use of many substances which might conceivably have imitated the main effects of cortisone and chlortetracycline, it became clear that the action of aspirin in this infection did not resemble that of cortisone or chlortetracycline and that chlortetracycline was not acting as a simple irritant, however important its irritant action undoubtedly was in enhancing the lesions when it was given along with *C albicans*

O'Grady and Thompson have certainly given us something interesting to ponder, even if neither they nor we can be quite certain of what it all means in terms of clinical medicine

ADOLESCENCE

THE consequences of human polymorphism in development-rate have lately been underlined once again by Tanner[1] By carrying out one of the first really large studies that included longitudinal as well as cross-sectional observations[2] Tanner has shown the extent of this polymorphism, which is seriously obscured if events at puberty are pictured from cross-sectional averages There is a large diversity in the patterns of change and the rates at which they occur over the period from 9 to 16 years of age by plotting the time of occurrence and range of onset of the spurts of fat deposition, height gain, genital development, and muscular strength, it can be seen that "an early-maturing boy may have finished his entire adolescence before a late-maturing boy of the same chronological age has even begun his first enlargement of the testis" This diversity—which is obvious from general experience once it has been pointed out, but for which astoundingly little allowance is made—has important educational implications Tanner also draws attention to the likelihood of psychological effects associated with late or early development in a given social setting The early developer may be precocious and popular (or alternatively precocious and embarrassed), the late may become despondent over his sexual or athletic inadequacies None of these will be constant effects—in different social settings they may operate to produce opposite results—but there seems little doubt that rate of development may be a more important determinant of personality than has generally been conceded Since, moreover, early or late puberty are likely, on animal evidence, to be heritable, possibly one should seek here the supposed "genetic" bases of various personality characters—homosexuality or excessive shyness, for example, which show twin and sib correlations

Tanner's work is a shining example of the realisation of human polymorphism—of the number of different "normalities"—which human biology is contributing to medicine The follow-up of these series into adult life will contribute still more It would be interesting to know, for example, whether rate of development and rate of senescence are positively linked, or negatively as in hybrid vigour, where hybrid animals both develop faster and live longer than inbred

THE RUSSIAN VACCINE

UNCERTAINTY about the Russian vaccine which has been used in the treatment of multiple sclerosis[1-3] is lessened by a letter in last week's *British Medical Journal* Writing from Moscow, Professor Shubladze and Professor Dick say that it is necessary to reinvestigate and characterise the original isolates of the SV strain of acute encephalomyelitis virus from which the vaccine of Shubladze and Margulis was prepared, because recent experiments have shown that the SV strain in current use is similar to rabies virus Further recommendation about treatment with the vaccine cannot, they add, be made until these new inquiries have been completed Dick and his colleagues in Belfast had earlier reported[4] results suggesting that the virus was rabies virus, and it is welcome news that Professor Shubladze and Professor Dick have been able, by personal discussion, to throw light on a confused situation

LIFE PEERS

THE traditions and institutions that survive longest are those that can assimilate and accept change with grace and realism, and for some time it has been apparent that the House of Lords was remaining dangerously unchanged in a changing world The reform now being undertaken is a further breach in the hereditary principle Already the Law Lords sit as life peers, and the Bishops only while they hold their sees, and now the number of life peerages is to be gradually raised, so that the House shall contain more members willing and able to devote a good deal of time to its business We are glad to note that the list of fourteen new life peers announced last week contains the names of two doctors

Sir John Stopford, as a past vice-chancellor of the University of Manchester, a fellow of the Royal Society, and an emeritus professor of experimental neurology, has the background of an administrator and a scientist Dr Stephen Taylor has already had some taste of politics as M P for Barnet from 1945 to 1950 Since then, to his war-time experience as the director of Home Intelligence and the War-time Social Survey, he has had added the knowledge of social medicine he has gathered from his special studies, on behalf of the Nuffield Provincial Hospitals Trust, of general practice and of the health service He is also director of the industrial health service of the new town of Harlow, in whose development he has played no small part

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Sir CLEMENT PRICE THOMAS has been elected president of the Welsh National School of Medicine

Professor A M CLAYE has been re-elected president of the Royal College of Obstetricians and Gynæcologists

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[1] Physical Maturing and Behaviour at Adolescence By J M TANNER, M D D.SC., D P M Published by the National Children's Home, Highbury Park, London, N.5 1958 Pp 46 2s 6d

[2] See Tanner, J M Growth at Adolescence Oxford, 1955

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[1] See *Lancet*, 1958, i, 730

[2] Liversedge L A *ibid* p 1224

[3] McCluskie J A W , Timburg, G C *ibid* p 1396

[4] Dick, G W A , McKeown, F , Wilson, D C *Brit med J* 1958, i, 7

Special Articles

BREAKING UP THE MENTAL HOSPITAL

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THREE years ago, Banstead Hospital housed 2450 patients, and there was a waiting-list. There are now some 2000 patients in the hospital and no waiting-list. Yet, during these years the annual number of admissions has risen by 40%, and the hospital's catchment area has grown, adding some 40,000 people to the population which it covers.

REFORMS AND RESULTS

These changes are largely due to our interpretation of the new outlook on the duties and responsibilities of the mental hospital.

We have assumed that all patients entering hospital come for treatment and expect to return to their homes. Therefore, every admission, however apparently hopeless the prognosis, has had active treatment and rehabilitation, whether he was a new patient, a readmission, or a geriatric patient. The only exceptions have been patients with a progressive organic dementia.

All admissions have been treated in fairly small wards, all of them open, with maximum privileges.

Instead of admitting all disturbed women patients to one ward as in 1955, we now admit them to four wards. One ward is reserved for the physically ill, the allocation of patients to the other three wards is determined partly by age and partly by diagnosis.

We have been in touch with relatives, friends, and employers, and asked them to ensure that a place in the community is kept open for the patient.

Physical treatment, particularly E.C.T. and the tranquillisers, is used extensively, not only to alleviate symptoms, but also to enable the patient to make full use of the therapeutic social activities we offer him.

We have started many social and occupational activities, of which the small factory within the hospital itself was one.

The nursing staff have, of course, played a large part in the changes. Two maxims have been of the greatest importance. The nurses have been encouraged to treat the patients on the understanding that "their patient today may be their neighbour tomorrow". Secondly, it was made clear to them that when a long-stay patient was made fit to resume life outside hospital, his place in the overcrowded ward would not be taken by another. Thus the nurses knew that success in their efforts to help a patient would mean an improvement in conditions. The old policy by which vacancies on long-stay wards were filled with more disturbed patients from elsewhere discouraged the nurses.

In 1955, not only were the wards overcrowded, but they were too big. Among twenty-six wards on the women's side we had seven with over 100 beds in each. As a result of our discharges and some rearrangement, no ward now has more than 60 beds, though this is still twice as many as we should like.

Another result of our discharge policy has been the development of our outpatient service, for we had to provide supervision and further treatment for more patients. Our outpatient clinics have all expanded—some as much as sixfold in the last three years.

PLANS AND PROPOSALS

One of the biggest problems in our present mental hospitals is their size. During the Victorian era when they were built, the policy was to provide custodial care and to house as many patients as possible as cheaply and conveniently as possible. The large barnlike wards therefore accommodated at least 100 patients, and each of the large prison-like hospitals held 2000–3000. We have made some progress in reducing the number of patients in a ward, but the 2000-bed mental hospital is much too large, however small the individual wards become. It cannot possibly form a "social field", in Lewin's sense, in which each individual influences the whole, and the whole influences each individual. No doctor or nurse can possibly know all the patients, and each person in the hospital inevitably feels relatively insignificant. We should aim at hospitals of 200–300 beds. Since these hospitals cannot at present be built, we have started to try to break up our present colossus into smaller, more manageable units. For example, we have now a 100-bed non-statutory unit which was originally built as an admission ward, and also a 100-bed unit for tuberculous men which serves the South West Metropolitan region. But we are still left with the main mass of the hospital, which on the women's side means 1200 patients shared between twenty-five wards.

There seems no obvious way of breaking up our ward blocks structurally, but we propose to divide them functionally, so that each unit provides a complete hospital service of its own. These hospitals within a hospital will each be run by a doctor who will be responsible for treatment and transfers within the unit. Each will have its own "matron" and nurses and ancillary workers.

We plan to break up our 1200-bed unit into three admission hospitals, each with 200 beds, a geriatric hospital with 300 beds, a hostel for patients working in the hospital industries, with 250 beds, and rehabilitation unit with 50 beds.

The three admission hospitals would be the *geriatric* unit (with 1 admission ward, 1 convalescent ward, and 2 wards for patients whose physical health is deteriorating and whose discharge is unlikely), a unit for *young, disturbed patients* usually with schizophrenia (with 1 admission ward and 3 wards providing graduated social training and rehabilitation), a similar unit for *middle-aged patients* of roughly forty to sixty.

Part of the proposed geriatric hospital already houses the most frail or physically ill of our long-stay senile population. In view of the present demand for geriatric beds and our ageing long-stay population we propose to bring the number of beds up to 300 so as to provide an adequate geriatric service for the long-stay wards in the hospital.

As many of our patients, though employable and needing practically no supervision, have not been able to find a suitable niche in the community, we provide accommodation for them within the hospital and this unit will become the proposed hostel. From these wards the patients go out in the morning to work in our factory projects or to do hospital domestic work. They eat in the hospital's self-service cafeteria. They take part in the social opportunities of the hospital and of the local community.

The small rehabilitation unit will be used for the active rehabilitation of patients from the long-stay wards who are planning to leave hospital in the near future. It will enable them to concentrate on their social problems, and when they move into this ward we shall be able to see their capacity to adjust to a new situation. As we are extremely short of social workers, the nurses on this ward will probably perform some of their duties.

DISCUSSION

When an unwieldy hospital is broken into smaller units, group and community techniques become feasible, morale improves, and patients and staff develop a greater sense of purpose and a clearer idea of their function in the therapeutic community But to obtain the best results each doctor should be in charge of a unit for not less than a year and preferably longer Under our present system, where the units are formed by segregating patients according to age or length of stay, doctors tend to have a restricted experience of inpatient psychiatry The benefits of our proposals are most obvious to the junior nursing staff, but they will exact a considerable change in attitude and function among the senior nurses, who have usually been trained for a different system of organisation and who can feel, justifiably, that much of their training and experience is now set aside, while fresh demands are made upon them

So far as we have been able to progress with our scheme, there seems no doubt that the patients benefit by it They have continuity of treatment and human relationships Their problems are no longer "lost" by transfer from one therapeutic group to another Under our scheme all parts of the hospital will have positive functions instead of merely providing beds

It should be made clear that the provision of hostel accommodation and sheltered workshops is *not* the proper function of a mental hospital These facilities should be in the community, and, though they need some psychiatric supervision, they should be run by the local authority Though many of our patients using our hostel and workshop have made an excellent social adjustment, it is an adjustment within hospital and their prospects of discharge are now lessened rather than increased, for the community outside can offer no improvement in their way of life

We expect the number of patients in the hospital to continue to fall at the rate of 100 a year, but this reduction could be greatly speeded if the local authority provided adequate aftercare services A hospital of 300–500 beds would probably suffice for the treatment and hospital care of the patients we are at present admitting Unless we are aware of this possibility and encourage the changes in attitude, both in the hospital and in the community, which will be necessary to achieve it, huge overpopulated unwieldy mental hospitals will continue to dominate psychiatric practice and absorb an increasing proportion of the health services expenditure

THE BRITISH DIET

In 1956 in this country the transition to a free market was almost complete, and the National Food Survey Committee's report [1] for that year is their first to record household diets under trading conditions similar to those prevailing before the war

Comparing 1956 with 1934–39, the biggest change is an increase of 37% in milk consumption Meat consumption is up by 3%, but fish is down by 16% A decline of 37% in butter is almost completely offset by an increase in margarine Cereals are down by 8%, but potatoes are up by 16% Fruit and vegetables are almost unchanged The nutrients available from these supplies show few significant changes Daily intake of calcium per head has gone up by from 688 to 1107 mg per day, derived partly from the extra milk and partly from artificial addition to bread Total calories have increased from 3000 to 3140 per day, protein from 80 to 83 g per day, and fat from 130 to 138 g per day (These figures take no account of the distribution of the food or of the inevitable losses in the wholesale and retail trade)

In 1956 the National Food Survey recorded the diets consumed in 9617 households involving 31,063 persons

The households were chosen to give a statistically valid sample of different social classes and of different parts of the country Special attention was paid to the income of the householder and to the proportion of the income spent on food, but the surveys do not cover food eaten outside the home, in restaurants and canteens

In all economic classes the average daily intake of all the nutrients is satisfactory as judged by the B M A Nutrition Committee's recommendations Differences between the social classes still exist, but these are much smaller than in the pre-war years, when at least 10% of the population were not getting a sufficiency of essential nutrient The figures show that no large section of the community are underfed, judged by modern physiological standards But, as the data collected covered less than 1 in 1000 of the population they do not exclude the possibility that a minority numbered in tens of thousands may still not be getting a physiologically adequate diet

Households dependent on old-age pensions and those with four or more children are the most likely to be underfed

In 1956, 245 households dependent on pensions and with an average total weekly income of less than £6 10s were surveyed The average expenditure per person in these households was 27*s* 10*d* The average physiological value of the diets consumed was satisfactory and this indicates that the majority of old people were getting enough to eat

The number of families with four or more children surveyed was 236 Again the average intake of nutrients was satisfactory, but the numbers—especially in the lowest economic group—were small It is recorded that the average weekly expenditure on food by an adult couple increased between 1952 and 1956 from 57*s* 3*d* to 72*s* 9*d*, whereas the regression estimate of extra expenditure for each additional child rose from 8*s* 6*d* to 8*s* 10*d* a week in the same period From these figures it seems reasonable to conclude that solitary couples have been able to keep up their usual food customs despite the inflationary period, whereas large families must have had to make considerable economies Yet there is no evidence that these economies have reduced the intake of nutrients below physiological standards

A large section of the survey has been devoted to geographical differences in the household diets

These differences seem of little or no public-health importance, though no doubt they will be keenly studied by the market-research investigators and may even divert a general reader The Welsh spent more money on butter than anyone else but much less on eggs than the national average In Scotland they spent much more money on cakes and biscuits, but less on fresh green vegetables than the average Londoners appear to have spent most on vegetables, fruit, and milk, and, despite the higher prices, to have consumed more The Midlands top the list easily for expenditure on cheese The North and Yorkshire are right at the top in expenditure on flour, suet, and dripping, and this seems to be the region to go to for home-made cakes The long table recording these differences deserves study by any family contemplating a holiday in lodgings and undecided where to go But on turning to the table where everything has been reduced to calories, carbohydrates, vitamins and the rest, the local interest has disappeared and uniformity at a satisfactory level is presented

A detailed appendix sets out quantitatively the different foods which are the source of fat in households of different economic class, in different geographical regions, and in relation to the number of children. This has been provided for the help of those epidemiologists who are looking for relationships between the nature of the dietary fat and the incidence of coronary-artery disease. The uniformity in the total quantity of fat consumed is striking, though (as already stated) the Welsh take much more in the form of butter. The intake of vegetable fat is also remarkably constant (20 to 25 g. per day) at all social levels, but there is a small increase in the average intake of animal fat (from 77 to 95 g. per day) in the higher economic groups. At first sight little of importance appears to have come to light in this analysis, and the committee themselves present little comment. The working out of the correlations, if any, between these figures and corresponding data for mortality-rates is a task for the vital statisticians.

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[1] Domestic Food Consumption and Expenditure 1956 Annual report of the National Food Survey Committee H.M Stationery Office 1958 Pp 172 9*s* 6*d*

The committee have now published records of our national diet covering the years from 1940 to 1956. Their reports are admirable summaries of the country's food intake and it is highly desirable that their surveys should continue. Perhaps, however, some variation in scope would be valuable. The committee seem so far to have concentrated on attempting to survey systematically all classes all over the country. It might be worth limiting such surveys to every third year, concentrating in the intervening years on one of the groups in which households may be especially liable not to get enough satisfactory food. Old-age pensioners and families with a large number of children are two such groups. Though they were surveyed in 1956, the numbers were too small to justify the assumption that all was well with their food-supply.

Public Health

Regrouping of Water-suppliers

In 1956 the Minister of Housing and Local Government called on water-suppliers to regroup themselves into larger and more efficient units.[1] Since then the number of undertakings in England and Wales has been reduced by 33 to 993 at the end of June. In addition, two compulsory orders and thirteen agreed orders, which together would reduce the undertakings by a further 36, were then awaiting the Minister's confirmation, the Minister had announced his intention of making three more compulsory orders, affecting 22 undertakings, and four private Bills were before Parliament.

The Minister has now called for speeding of regrouping,[2] saying that he will not hesitate to use his compulsory powers if suppliers cannot reach agreement among themselves.

Second Quarter in England and Wales

The birth-rate in England and Wales in the June quarter was high and the infant death-rate low.[3]

Live births numbered 189,159, a rate of 16·9 per 1000 population, the highest rate for a June quarter since 1949 when the rate was 17·6. Deaths numbered 124,113, a rate of 11·1 per 1000 population. The rates in the June quarters of 1957 and 1956 were 10·6 and 10·8 respectively. Deaths of children under one year of age totalled 4030, giving a record low rate for a June quarter of 21·3 per 1000 live births. The previous lowest for this quarter was 22·3 last year. In 1938 the corresponding figure was 50·3.

Anti-fly Campaign

An anti-fly campaign was held in Canterbury from July 14 to 19. The campaign included posters, the use of a loudspeaker car that toured the streets, and a competition for the best-kept dustbins. The schoolchildren were awarded prizes for the best short essays on What I Think We Should Do About Flies.

Conferences

ANÆMIA AND THE ALIMENTARY TRACT

Last week the Royal College of Physicians held the first of its new college conferences, with 117 participants, of whom 21 were invited speakers. Prof. Robert Platt, the president, explained that the programme had been arranged by Prof. L. J. Witts, Prof. J. V. Dacie, and Dr. F. Avery Jones, and that the speakers had been selected from among those who are actively extending knowledge of anæmia in its relation to the alimentary canal. Chairmen at the sessions were the President, Dr. T. C. Hunt, Professor Witts, and Dr. T. L. Hardy.

The Mouth and Œsophagus

Dr. Richard Asher (London) pointed out that the tongue is to some degree an index of the state of the rest of the alimentary tract, especially in sprue. Glossitis indicates that there is something wrong, but gives little clue to what it is, for atrophy occurs both in iron-deficiency anæmia and in pernicious anæmia, though in the latter the tongue usually appears glazed and glossitis precedes the anæmia, whereas in iron deficiency there are changes in the lips and angular stomatitis. There is doubt whether the atrophic changes in iron deficiency are due to the iron deficiency, for deficiency in any of the vitamin-B group may be followed by papillary atrophy and then by iron deficiency, while the lesions can be cured with riboflavine or with iron.

Dr. Asher recalled that A. B. Kelly and D. R. Patterson gave a full description of dysphagia associated with iron deficiency and a tendency to carcinoma of the œsophagus no less than three years before the inadequate description given by Vinson and the private communication of Plummer.

Dr. Wilfred Sircus (Edinburgh) discussed aphthous stomatitis and the syndromes of Behçet, Reiter, and Stevens-Johnson. About 20% of the population suffer sometimes from aphthous stomatitis—females twice as often as males—and nearly a fifth of the sufferers have attacks so frequent as to be virtually continuous. These ulcers can become confluent and cause severe scarring. Lesions occur on the genitalia in half the female but only 2% of male sufferers. The pathology is non-specific, but an inquiry showed that two-thirds of patients with malabsorption states had previously had severe aphthous ulceration, while 70% of sufferers from aphthous stomatitis suffered from severe anxiety states or emotional conflicts and nearly 60% were depressed. The ætiology is uncertain, but a metabolic or autoimmune process now seems more likely than a virus infection.

Behçet's syndrome is indistinguishable except that it involves the conjunctivæ and vagina: oral ulcers may precede the other lesions by several years. Recurrent herpes tends to die out as the patient gets older. Reiter's disease associates oral ulceration with urethritis and conjunctivitis. Oral pemphigus is painless but leaves lacy scars, and epidermolysis bullosa is rare. The Stevens-Johnson syndrome when fully developed has a generalised rash, with ulceration of face, mouth, conjunctivæ, and genitalia, but sometimes the lesions may be less extensive; if confined to the mouth, a macular rash develops vesicles which in 5–6 hours fuse to form bullæ, then burst and form serpiginous infected ulcers with a necrotic base and a hæmorrhagic margin.

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[1] See *Lancet*, 1956, ii, 728.
[2] Circular 4/58.
[3] The Registrar General's Weekly Return no. 29, 1958. H.M. Stationery Office. Pp. 20. 1s. 6d.

Dr T D Kellock (London) discussed œsophageal lesions, pointing out that in the "Plummer-Vinson" (Kelly-Patterson) syndrome the anæmia seems to cause the lesion, whereas in hiatus hernia the lesion causes the anæmia In the Kelly-Patterson syndrome complete restoration to normal health is unusual (4 of 26 cases), the web remaining Rare cases of œsophageal web without anæmia or dysphagia have been seen, and it may be that the web formation is a congenital lesion and not, as hitherto thought, a consequence of iron deficiency However, 3 male patients have developed the syndrome apparently from chronic bleeding at the suture line of a gastroenterostomy, and these may be the heralds of an epidemic of this syndrome due in 15 or 20 years as a consequence of the many gastrectomies performed nowadays Among patients with hiatus hernia, anæmia is common only in the rolling (55%) or combined (28%) types Peptic ulceration of the œsophagus is rare, and occurs exclusively in heterotopic mucosa, the commonest objective finding is anæmia

In the discussion it was brought out that smooth tips to the tongue may be considered normal and that new methods of tongue biopsy may help The absence of a control series of housewives without aphthous ulcers was criticised and the excellent results of treatment with hydrocortisone emphasised

The Stomach

Prof H A Magnus (London) described the histopathology of the stomach in pernicious anæmia By the time death occurs there is severe atrophy of all coats of the stomach, often with replacement of the body mucosa by intestinal epithelium and always without any evidence of inflammation However, now that the changes can be observed during life by using Wood's gastric biopsy tube, the picture has changed Only 40% of patients show complete atrophy, 35% show severe atrophic gastritis, 16% atrophic gastritis of less advanced degree, and 9% severe gastritis with atrophy but survival of a variable proportion of chief and parietal cells, even after pernicious anæmia had been present for several years He concluded that there is a progressive inflammatory atrophic gastritis, and that this ultimately leads to complete gastric atrophy, the inflammation need not be exogenous Such stomach changes are not confined to pernicious anæmia, but if a patient with such changes lives long enough he will probably develop pernicious anæmia He also thought that a genetic nature is suggested by the history of the 20 cases of the juvenile pernicious anæmia

Dr Margot Shiner (London) described Wood's gastric biopsy tube and the intestinal biopsy tube The procedure is not entirely devoid of the risk of hæmatemesis (3%) but has never caused anxiety for the patient's life In the stomach she differentiated between gastric atrophy and atrophic gastritis of varying degrees, and in the intestine she noted varying degrees of villous atrophy with hyperplasia of the glands of Lieberkuhn Idiopathic steatorrhœa and cœliac disease display severe villous atrophy irreversible on treatment, whereas in tropical sprue and most cases of postoperative steatorrhœa the villi do regenerate when the patient is effectively treated In pernicious anæmia and in iron-deficiency anæmia the intestinal mucosa is normal, but stomach mucosa is atrophic, or atrophic gastritis is present, in all patients with pernicious anæmia, in 54% of those with iron deficiency, and in many patients with idiopathic steatorrhœa These results seem compatible with the hypothesis that pernicious anæmia is the final result of a genetically determined progressive atrophy of the chief cells of the gastric mucosa, while cœliac disease and idiopathic steatorrhœa result from an analogous atrophy of the crypt cells of the intestinal mucosa

Dr R O K Schade (Newcastle) described his technique of gastric lavage for the diagnosis of carcinoma of the stomach by exfoliative cytology The best results are obtained in early cases because after ulceration the cytological details are often obscured by debris In four years, 30 cases were diagnosed by this method when other methods failed, and in 13 the tumour was microscopic and had not started to invade Several patients had a small carcinoma as well as a peptic ulcer

In the discussion the general opinion was that exfoliative cytology of the stomach seems justified in any patient with unexplained gastric disturbances, and that although false positives may occur this procedure is the only one which can detect early cases of gastric carcinoma The cost of such tests on a large population was considered, but Dr Schade thought that it need not be excessive

It became clear that the recent work on megaloblastic anæmias has left some confusion about the best definition of pernicious anæmia in modern language Dr Sheila Callender (Oxford) said that in cases of pernicious anæmia there was evidence that one parent or the other had latent or expressed pernicious anæmia, and Professor Magnus suggested that the disease be defined as a megaloblastic anæmia occurring in a subject with a congenital chemical defect causing a progressive gastric lesion which normally continues to complete atrophy

Investigation of Gastric Secretion

Dr K B Taylor (Oxford) described the simplest indirect methods of measuring gastric secretion—the 'Diagnex' tests of gastric acid production, which can be done without passing a gastric tube, and the estimation of uropepsinogen excretion

Neither the quininium nor the azure A diagnex resins give complete correspondence with the histamine test meal Pyloroduodenal obstruction, syndromes of small-intestinal malabsorption and hurry, gastric operations, and disease of the urinary tract may affect the results, and gastric stimulation with caffeine sodium benzoate may be inadequate Even when these possible sources of error have been excluded, false positive and negative results occur The latter are unimportant, provided they are always checked by a subsequent maximal histamine test meal, but false positives are unsatisfactory In this respect the quininium test is better than the azure A, and the positive error is only 5%, which makes it a useful screening procedure in clinical diagnosis, where a finding of achlorhydria suggests pernicious anæmia or gastric carcinoma (or both) and excludes duodenal ulcer, and a finding of free acid excludes pernicious anæmia In research the test is valuable in picking out patients with defective gastric secretion

The uropepsinogen test is even easier to perform, requiring only the collection of a twenty-four-hour specimen of urine and the estimation of proteolytic activity by a comparatively simple method The levels of uropepsinogen in the urine of patients with pernicious anæmia are always very low, but similar levels may occasionally be found in subjects in whom other tests of gastric function are normal Thus the chief usefulness of the test in research is in screening subjects for more detailed investigation of gastric function, and in Oxford this has proved to be the most satisfactory single test In clinical diagnosis, since a high result excludes pernicious anæmia, it has a real value in the investigation of patients who have received treatment with vitamin B_{12} and are no longer anæmic, and in whom there are reasons for questioning the diagnosis of pernicious anæmia

Mr A W Kay (Glasgow) gave an entertaining and complete account of his augmented histamine test, showing how he established in this test that maximal histamine response occurs, by means of dose-response curves He emphasised the importance of performing the test in a standard way, paying particular attention to the time factor The maximal gastric secretory response lasts about 30 minutes and is attained 15 minutes after subcutaneous injection of histamine There was remarkable quantitative correspondence when repeated tests were done in the same subject His experience is that most patients who show no change in the pH of the gastric contents with his test have pernicious anæmia He believed, that the test is of value in determining how much of the stomach should be resected in operations for peptic ulcer, but he was dubious of its value in the diagnosis of gastric carcinoma The most interesting results he presented were of the effects of antrectomy and vagotomy on the secretion of acid by the stomach Both procedures markedly reduce acid secretory response to maximal histamine stimulation, though the number of parietal cells is unaffected Finally, Mr Kay agreed with Dr Taylor that true achlorhydria is uncommon and requires further investigation

The discussion was opened by Dr Sircus, who regarded the augmented histamine test as a major advance in investigation of gastric function In Edinburgh they have noted that steroid therapy often results in an increased response of acid secretion to histamine Dr Avery Jones (London) mentioned a patient who had hypersecretion of acid and showed no increased response to histamine this was possibly due to a secretory islet-cell tumour of the pancreas Mr Kay said he had had a similar case Professor Witts (Oxford) said that if achlorhydria is found with the histamine test it may be due to faulty positioning of the tube, and that fluoroscopic control should be done Other points discussed were the action of the antihistaminic drugs when used in the augmented histamine test, the observation by several observers that in pernicious anæmia there may be a small rise rather than a fall in the pH of gastric juice on histamine stimulation, and the value of direct measurements of pH in the stomach, using electodes in situ Mr Kay's opinion on this last method was that the results are too variable to be useful

Investigation of Anæmia

Dr Sheila Callender said that estimations of serum-iron levels alone are of little value in assessing whether a subject is iron-deficient the iron-binding capacity of the serum should be measured as well In this way, iron deficiency can be detected even in the absence of anæmia, (the *sideropænia sine anæmia* of Waldenstrom), when there is a low serum-iron level with normal or raised iron-binding capacity The value of radioactive isotopes of iron is in assessing absorption, utilisation, and turnover of iron Absorption can be measured by giving a test dose of labelled iron (and here the size of the dose is important) and measuring the amount excreted in the fæces, or by giving, contemporaneously, an intravenous dose of a second isotope of iron, and measuring the rate of disappearance of both oral and intravenous isotope from the plasma In this way a corrected plasma curve for the oral isotope can be obtained, from which can be calculated the amount absorbed from the gut Dr Callender went on to discuss the use of foodstuffs labelled with radioactive iron Such tests better reproduce normal conditions than giving a small dose of inorganic iron to a fasting patient The best test is to give a normal bulk of food with the labelled material In this way it has been shown that food iron absorption is reduced after gastrectomy, and this has cleared up the very important problem of postgastrectomy anæmia

Tests of absorption have shown that, except in steatorrhœa and after gastrectomy, the commonest cause of chronic iron-deficiency anæmia is blood-loss A " primary " failure to absorb iron is exceedingly rare Finally, she thought that in-vivo counting of radioactive iron has little value, except in the diagnosis of myelosclerosis, where counts over some site of high marrow activity, such as the sacrum, may be abnormally low

Dr D L Mollin (London) gave an account of his experience with serum-vitamin-B_{12} estimations, and the use of vitamin B_{12} labelled with radioactive cobalt, in studies of absorption The serum-B_{12} concentration, measured microbiologically by the *Euglena gracilis* method, is the best indicator of deficiency If there is deficiency of the vitamin the absorption studies, using the fæcal excretion test, or the urinary excretion test of Schilling, can be done He presented evidence that in subacute combined degeneration of the spinal cord the vitamin-B_{12} concentration in the serum tends to be lower than it is in pernicious anæmia, and that in the former, with marked B_{12} deficiency, there may be no anæmia Patients with anatomical lesions of the small bowel, such as strictures and loops, show low levels of serum-B_{12}, mostly in the pernicious-anæmia range Absorption of the vitamin is impaired and is improved only by giving antibiotics orally When the ileum is involved, there is no way of enhancing absorption, since this structure is the main site of absorption of vitamin B_{12}

Many patients with idiopathic steatorrhœa, sprue, and tropical macrocytic anæmia have low serum-B_{12} levels, but fail to respond completely to the vitamin and require folic acid as well

Professor Dacie (London) completed the session by describing experiences at Hammersmith Hospital with tests of folic-acid clearance and folic-acid absorption Dietary deficiency of folic acid is rare The types of megaloblastic anæmia which are benefited by folic acid are those associated with idiopathic steatorrhœa, sprue, pregnancy, anticonvulsant therapy, leukæmia, cirrhosis, and kwashiorkor He went on to give details of the intravenous folic-acid clearance test which seems to be a good indicator of folic-acid deficiency Thus, in steatorrhœa with megaloblastic anæmia but normal serum-B_{12} levels the rate of fall in concentration of the injected folic acid is much higher than normal In megaloblastic anæmia associated with mysoline therapy the fall-off is normal, which suggests here that the underlying defect is one of utilisation In pernicious anæmia there may or may not be concomitant folic-acid deficiency, and the test cannot distinguish between it and megaloblastic anæmia due to folic-acid deficiency alone Professor

Dacie concluded by giving an appraisal of the test of folic-acid absorption developed by Dr Chanarin, which depends on measurements of folic-acid concentration in the serum after an oral dose, the patient being saturated with folic acid previously

One of the points raised in the discussion was that radioactive iron studies alone are of no value in assessing whether splenectomy should be done or not, when there is other evidence both of splenic erythropoiesis and red-cell destruction Dr W T Cooke (Birmingham) gave his opinion that the rate of disappearance of folic acid from the serum after injection should not be interpreted in terms of tissue desaturation Dr I Chanarin (London) said that in his experience rapid clearance of folic acid occurs only where deficiency may be expected Professor Witts wound up the session by saying that in clinical practice estimations of serum-vitamin-B_{12} are seldom of value, because the patient has nearly always been given some vitamin B_{12}, that in anomalous cases labelled vitamin-B_{12} absorption tests may be useful if available, and that the application of the folic-acid tests is almost wholly a research procedure

Steatorrhœa

Dr W P H Sheldon (London), speaking on cœliac disease, said that the more severe it is, the greater is the anæmia—usually hypochromic and responding somewhat indifferently to oral iron Of 81 patients, 7 (9%) had a megaloblastic anæmia which responded promptly to folic acid He laid stress on the importance of Dr Shiner's biopsy findings and the need for further data The chief advance in knowledge, however, has been the discovery of the effect of gluten A gluten-free diet is not particularly palatable to the child, so the taste of wheat products should be retained by using gluten-free wheat starch Gluten is broken down into gliadin and glutamine, and the noxious agent is in the gliadin, but tryptic digestion to peptides does not remove it Digestion with hog's stomach does The actual substance seems likely to be a peptide-glutamine complex which may well act directly on the organs rather than only on digestion—e g , on mental processes and on growth The rate of growth increase when a child returns to a normal gluten-containing diet will show whether he has acquired tolerance for gluten Of 95 patients treated for eighteen months or more on a gluten-free diet, 72 continued normal growth when reverting to gluten, 11 relapsed, with full symptoms, and 12 showed intolerance only by slowing of growth

Dr W T Cooke (Birmingham) would discourage the use of such terms as malabsorption syndrome, sprue, and jejunoileal insufficiency, because the various clinical states associated with disturbances of the small intestine are taking on distinctive patterns, some with features not necessarily due to malabsorption but rather to malutilisation Moreover, the term adult cœliac disease might be used to denote idiopathic steatorrhœa (with its implication that steatorrhœa is the most important factor), or non-tropical sprue (with its implied ætiological association with tropical sprue) It is justifiable to regard tropical sprue, with its different response to treatment, biopsy findings, folic-acid metabolism, and prognosis, as a specific clinical entity In all but the occasional patient three investigations are needed for a diagnosis of steatorrhœa In patients taking a normal mixed diet, a daily fat content of more than 6 g in stools collected for three to six days can be considered abnormal Careful radiological examination, with either flocculating or non-flocculating barium, is essential, for only by this method can many patients with apparently similar clinical symptoms be differentiated Thirdly, complete hæmatological investigation is required A persistently normal blood-count is strong evidence against adult cœliac disease Patients with steatorrhœa due to pancreatic lesions rarely have anæmia unless they are also malnourished The anæmia of adult cœliac disease is due to iron, vitamin-B_{12}, or folic-acid deficiency, either separately or combined Upsets in folic-acid metabolism are important Low serum-B_{12} levels are found in rather more than half the patients In regional ileitis, 42 patients out of 80 had low serum-B_{12}, and the impaired absorption could almost always be restored by steroid therapy The finding of 12 megaloblastic anæmias in 130 patients with regional ileitis again emphasised the importance of radiology Among the laboratory examinations, glucose-tolerance tests and carotene and vitamin-A tests give little help, but the xylose-tolerance test appears useful in separating the patients with adult cœliac disease from the other disorders Jejunitis, with its tendency to resolve, may simulate adult cœliac disease, since absorption of folic-acid in the jejunum may be grossly deficient Three more recent investigational techniques—intestinal biopsy, the folic-acid excretion test of Girdwood, and the response to gluten-free diets—make it evident that adult cœliac disease is a distinct clinical entity It is probably a familial constitutional enzymatic defect, embracing the pteroylglutamate complexes, though whether it is sited in the intestinal cell or in the liver is not evident

Dr J Badenoch (Oxford), after reviewing earlier observations on the anæmias associated with stricture and blind loops, described his own work on the intestinal diverticula He laid stress on the occurrence of diarrhœa, though only half the patients had steatorrhœa Some patients will present with anæmia indistinguishable from pernicious anæmia and be so treated The necessary radiological studies are sometimes difficult because the barium does not enter the narrow-necked diverticula Surgical treatment is unsatisfactory and it is better and safer to treat these patients by medical means Vitamin-B_{12} should be given monthly, and daily supplements of calcium gluconate 15–20 g , folic acid, and vitamins In the acutely ill patient, broad-spectrum antibiotics should be administered, but Dr Badenoch did not favour their continued administration Prednisone may also bring about remission

In the discussion, Professor A W Woodruff spoke of the difference in prognosis between tropical sprue and the disorders occurring in temperate climates Dr Callender reported dramatic increase in iron absorption in cœliac disease treated with prednisone, and in a child the initiation of gluten-free diet increased the absorption from 2% to 40% Dr A Doig (Edinburgh) recalled Girdwood's demonstration that bacteria from intestinal diverticula will take up vitamin B_{12} but actively produce folic acid

Dr P B B Gatenby (Dublin) said that, in reports on the treatment of iron deficiency, ferrous sulphate, ferrous gluconate, and ferrous succinate had all apparently induced much the same rate of hæmoglobin synthesis, but intolerance—possibly due to a higher dosage—was much commoner with ferrous sulphate Among 4000 pregnant women he found 350 with a hæmoglobin below 10 g per 100 ml Of these, 300 could take ferrous sulphate with good results Of the 50 who were intolerant, 20 did not benefit from other oral iron preparations and needed parenteral administration In late pregnancy the rate of hæmoglobin regeneration is much the same whether intravenous or intramuscular iron preparations are used, but on the whole 'Imferon' is the treatment of choice The indications for parenteral therapy are gastric intolerance, gastrointestinal disease (such as ulcerative colitis), certain types of steatorrhœa, rheumatoid arthritis, late pregnancy, and possibly for the replenishment of iron stores in recurrent anæmia

Prof L J Davis (Glasgow), whose paper was read in his absence, had reviewed 374 megaloblastic anæmias under his care in 1948–51 Of these 315 had pernicious anæmia the other diagnoses were malabsorption states (20), pernicious anæmia in pregnancy (16), nutritional deficiency (5), and anticonvulsant therapy (1), leaving 17 undetermined Of 73 patients treated with vitamin B_{12} by mouth combined with intrinsic factor, 20 relapsed He concluded that oral preparations are unsatisfactory and that regular parenteral therapy with B_{12} is best. He recommended 1000 µg followed by 250 µg weekly until blood-levels are normal, and therafter monthly 105 patients were treated with single doses of 1000 µg every three months, but by the end of this period their serum-B_{12} was approaching abnormally low levels He emphasised the dangers of folic acid in these patients and described the blunderbuss therapy sometimes advocated

Dr C F Hawkins (Birmingham), speaking of steatorrhœa, referred to the difficulty of assessing results of treatment in a condition which can show such dramatic and unexpected remissions With the usual restriction of fat and a high-protein diet, at least 70% can expect to be well enough to do their work satisfactorily Steroid therapy brings temporary improvement, but relapse is likely when it is discontinued In conjunction with Dr J M French, he has obtained clinical cure in 16 out of 22 patients Often this effect was quickly manifest, though it could take months Most striking was the effect on the incapacitating weakness and lassitude In all patients the blood-picture became essentially normal without any other therapy He ascribed failure of a gluten-free diet to four causes—the wrong diagnosis, insufficient time, incomplete diet, and unknown reasons As to these last, intestinal allergy might possibly explain the radiological pictures, a folic-acid deficiency might be present, or there might be an upset of glutamine-peptide complex

In the discussion, Dr Discombe wondered whether it was necessary to aim at a 1 2% increase of hæmoglobin per day when half this is sufficient He gave 65 mg elemental iron (one tablet) daily for six months to blood-donors who were anæmic Their hæmoglobin was restored to normal in three months and he had no difficulties with intolerance

Alimentary Bleeding

Dr George Discombe (London) discussed tests for occult blood in the fæces Benzidine has caused bladder cancer in those engaged in its manufacture and will therefore become a "museum piece" Its place can be taken by orthotolidine, which gives better results Dr Discombe has found both 'Occultest' and 'Hæmtest' tablets satisfactory The former is much more sensitive, and he favours a sensitive test for occult blood Those with a positive result can then be carefully examined with dietary and medicinal precautions He felt that the number of false positive results from the peroxidase in the stools had been exaggerated, but to ensure accurate results it is necessary to render oxidising enzymes inactive. In the Harrison benzidine test this has been achieved by boiling, which has always been the most troublesome feature of the test. Treatment of the stools with 1% sodium azide (a poison) provides an alternative and easier way of inactivating peroxidase Dr Discombe then described some promising but provisional results of testing for occult blood with orthotolidine after preliminary treatment of the stools with sodium azide If these results are confirmed, a test will be available whereby it will be easy to test for occult blood in the side-room—"safer, cleaner, quicker and cheaper" than testing in the laboratory

Professor Witts, speaking on anæmia after gastric operations, estimated that since 1948 some 100,000 persons in England and Wales must have undergone a partial gastrectomy As iron-deficiency anæmia almost inevitably follows this operation, the problem must be a considerable one The importance of bleeding in the ætiology of such anæmia is disputed It may be episodic, and a sudden fall in the hæmoglobin after operation should suggest blood-loss But the main mechanism seems to be a failure in the absorption of iron Though partial gastrectomy reduces the size of the stomach and the amount of hydrochloric acid it secretes, experiment has shown that there is no defect in the absorption of organic and inorganic iron (given on an empty stomach) The diminished absorption seems to be due to the impaired function of the stomach as a "hopper" for holding iron and food while the iron is converted from the ferrous to ferric state and absorbed Another contributing factor is the reduction in the amount of food which people take after gastrectomy Any gastrectomy will reduce the area secreting intrinsic factor, and after partial gastrectomy such persons tend to have a low level of serum-B_{12}—though (in those cases with a macrocytic anæmia) not quite so low as in true pernicious anæmia

In iron-deficiency anæmia after partial gastrectomy, parenteral iron is often the treatment of choice If iron is given by mouth, it should not be given in tablet form, for the tablets may be irritating and may hurtle through the stomach.

Pernicious anæmia is inevitable after a total gastrectomy, but relatively few cases are seen, because (1) resections are very seldom absolutely complete and (2) others are often treated with vitamin B_{12} from the time of operation B_{12} should be given in all these cases, supplemented with iron, though iron deficiency is not such a special problem in these cases as after subtotal gastrectomy If there is no response to B_{12} and iron, the possibility of a blind-loop syndrome should be considered

Dr Avery Jones reviewed the problem of unexplained hæmorrhage from experience of 2526 cases of alimentary hæmorrhage admitted to the Central Middlesex Hospital in 1941–47 He emphasised the importance of what he termed the "acute lesion group" as a cause which will be missed unless early gastroscopy is carried out This group accounted for nearly a third of those in his series The lesion is usually an acute ulcer but occasionally a gastrostaxis may be found—not infrequently around a stoma Acute ulcers most often occur on the posterior wall or the lesser curvature, they have an equal sex incidence, but in men appear more likely to become chronic. With early gastroscopy and a careful search for general medical causes of alimentary hæmorrhage, he was able to explain the cause of the hæmorrhage in half the cases in the X-ray-negative group But he emphasised the importance of following-up this group, for he has later been able to show a lesion in 24% of these cases—usually a peptic ulcer but even some new growths

An exhaustive list of the causes of alimentary hæmorrhage included food allergy a fellow of the college has a hæmatemesis each time he eats onions The Mallory-Weiss syndrome can be diagnosed by a history of vomiting, from whatever cause, followed by the vomiting of bright red blood from splitting of the longitudinal fibres of the lower œsophagus Among other disorders, von Willebrand's disease should be considered as a possible cause of recurrent bleeding, and pseudoxanthonum elasticum is a rare possibility Aspirin plays a significant role in bleeding, not only by producing an acute lesion but also in provoking a chronic ulcer to bleed It may also be found to be the cause of unexplained cases of recurrent anæmia

In reply to a question by Professor Witts, Dr Avery Jones gave advice on what to do about the difficult case of recurrent alimentary hæmorrhage for which no cause can be found after careful investigation He advised a laparotomy at the time of bleeding

PÆDIATRIC SURGERY

A striking feature of the meeting of the British Association of Pædiatric Surgeons held in London last week under the presidency of Miss Isabella Forshall was its cosmopolitan character This was particularly evident at the dinner in the Apothecaries Hall, when brief speeches were made by representatives of many European countries, as well as Japan, Australia, and the United States [1] Several countries were able to report growing recognition of the importance of pædiatric surgery, and the recent appointment of Mr A W Wilkinson to the newly created chair of pædiatric surgery in London was evidence to those from abroad that such recognition is not lacking in this country

Respiratory Emergencies

For his Moynihan lecture at the Royal College of Surgeons Dr Willis Potts (Chicago) chose the subject of Respiratory Emergencies in the Newborn In some infants, he said, the emergency is recognisable as such and the urgency of treatment is unassailable Among this group he described cases of tension pneumothorax or tension cyst where a child's life can be saved by aspirating 50 c cm of air from the chest and having the needle and syringe ready for a further aspiration should this be necessary before definitive treatment can be established Another condition in which the urgency is sometimes overlooked is congenital diaphragmatic hernia The amount of bowel in the chest may not be sufficient to cause serious distress at first, but any sudden increase in intra-abdominal tension can force more bowel into the chest, and kill the child in next to no time The one special examination which is likely to help more than any other is a good upright anteroposterior and lateral X-ray film of the chest, and the emphasis in this sentence is on the two words " upright " and " good " A horizontal radiograph is far less useful, and a poor radiograph may make it impossible to distinguish between cases in which major surgery is essential and others where less radical measures may suffice

The preoperative and postoperative management of the newborn in respiratory distress is going to depend very much on the quality of the resident medical staff and the nursing staff, and Dr Potts drew attention to the importance of having an emergency tray with endotracheal tubes, fine plastic suction tubes, and above all a laryngoscope in every ward in which these infants are cared for Such apparatus is useless unless the medical staff who are first called to the child by the ward sister are adept at laryngoscopy and the insertion of an endotracheal tube in infants Every resident in a department dealing with surgical problems in infancy should know how to handle this instrument

Meningoceles

If the Moynihan lecture by Dr Potts was directed mainly to management of conditions endangering life, several papers were concerned with the rehabilitation of infants suffering from spina bifida and its complications How often a mother brings a child to the outpatient clinic at the age of 3 or 4 years with a large meningocele, hydrocephalus, deformed legs, and an infected dilated urinary tract, with the story that the doctor told her that the baby would die before 9 months of age, or that the welfare clinic assured her that she would not rear him above 2 years of age! In his review of spina bifida cystica Dr K M Laurence drew attention to the large number of cases who are certainly alive at 8 years of age and may well live very much longer This should bring to all those who meet this serious incapacitating condition the realisation that they should help these children as much as possible The meningoceles can be dealt with in the neonatal period, and there is something to be said for this instead of leaving them until 18 months or 2 years of age as advocated by Ingraham and Motson True, the child may develop hydrocephalus, but, thanks to the pioneering work of Spitz in Philadelphia there is a good chance of controlling this condition and allowing brain development to take place The technique of inserting a Spitz-Holter valve was demonstrated at the meeting, and this procedure is now done in three or four centres in this country

Two aspects of myelomeningocele which are usually neglected are the problems of the bladder, and the problems of the lower limbs Mr D F Ellison Nash has put forward suggestions for the management of these babies, and there is little doubt that attention should be paid to the bladder at the earliest possible moment so as to prevent the infection of residual urine He described his technique for plication of the urethra, which has some place in bladder control in these serious cases

Mr W J W Sharrard propounded some stimulating views on the dislocation of the hip which so often accompanies myelomeningocele He had come to the conclusion that this was essentially a paralytic dislocation, since the muscles which were paralysed were exactly the same as those which are paralysed when dislocation of the hip complicates poliomyelitis

The management of this dislocation must therefore be based on principles differing from the management of the ordinary congenital dislocation of the hip, and Mr Sharrard was able to demonstrate that a well-thought-out and long-term plan of treatment would give some of these infants the chance of standing upright and walking

Œsophageal Atresia

In his Simpson-Smith lecture, delivered at the Hospital for Sick Children, Great Ormond Street, Dr Willis

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[1] After Sir James Paterson Ross had replied for the Guests, the following spoke informally Dr Yanagisawa (Tokio), Prof Fritz Rehbein (Bremen), Dr Hartl (Linz, Austria), Dr Wanda Poradowska (Warsaw), Dr Kafka (Yugoslavia), Dr Mázal (Brno, Czechoslovakia), Dr Willis Potts (Chicago), Prof A J Craig (Malta), Dr Matti Sulamaa (Helsinki), Dr Petterson (Göteborg, Sweden), Dr Juan Lestache (Madrid), Professor Soave (Genoa, Italy), Mr Russell Howard (Melbourne, Australia), Prof Max Grob (Zürich, Switzerland), Dr Akkary (Alexandria, Egypt), Dr D Vervat (Rotterdam, Holland), Dr Winkel-Smith (Copenhagen, Denmark), Dr N Tzemailas (Athens, Greece)

POTTS discussed the factors which had contributed to the gradual lowering of mortality in the treatment of œsophageal atresia in his unit so that the recent figures showed that three out of four patients were surviving In his large series of 148 cases, Dr Potts was able to pick out a number of factors which he thought had contributed to the improving results

The following morning, Prof **FRITZ REHBEIN** (Bremen) discussed the complications in the treatment of œsophageal atresia and Mr **R B ZACHARY** (Sheffield) presented two cases of complete absence of the œsophagotracheal septum During the discussion on these cases, and on Dr Potts' lecture, the discussion centred round many aspects of the treatment of œsophageal atresia including the choice of transpleural or retropleural approach, the routine use of a fine polyethylene cannula through the nose and down the œsophagus into the stomach for feeding purposes, and the problems connected with anæsthesia

SARCOIDOSIS

AN international symposium on sarcoidosis, arranged by the British Postgraduate Medical Federation, was held in London from June 30 to July 2

Dr **L SILTZBACH** (New York) felt that a definition of sarcoidosis should include the following reference to the Kveim test

> "The intracutaneous Nickerson-Kveim test employing a sarcoid tissue suspension of known activity and specificity is microscopically positive in a majority of instances among patients with florid lesions The test is of value in the absence of other tissue biopsy confirmation of the diagnosis or when clinical and histological findings conflict"

Dr **J G SCADDING** restricted himself to a morbid-anatomical definition to include the tissues most frequently involved and the histological changes observed in those tissues Dr **A D THOMSON** pointed out that a pathologist could only report that the histological changes were consistent with the diagnosis of sarcoidosis, for sarcoid tissue was a non-specific response to a variety of agents Dr **O REFVEM** (Oslo) enumerated several chemical, infective, and neoplastic processes known to provoke these local sarcoid-tissue reactions In reviewing the vexed problem of ætiology, Dr **J TURIAF** (Paris) opposed the view that sarcoidosis was related to tuberculosis

Epidemiology of the disease in Great Britain has so far been unrewarding, but Dr **J CHAPMAN** (Dallas, Texas) surveyed its global distribution Dr **M CUMMINGS** (Washington) provided interesting data based on its prevalence in the South-Eastern region of the United States He and his coworkers have long been aware that forested areas might provide some clue More recently they have observed that pine pollen has certain chemical similarities to the tubercle bacillus, including acid-fast staining properties A pine-pollen extract provoked delayed-type (tuberculin-type) skin-test reactions in half of a group of patients with sarcoidosis, and it also produced local tuberculoid granulomas in animals Further immunochemical and epidemiological investigations are in progress to definite the substance and its possible role in the disease Dr **W G STRAWBRIDGE** (Cardiff) drew attention to a long-chain fatty acid which he had uncovered in sarcoid tissue Interesting and important work remains to be done to define the relationship of this substance to Dr Cummings' pine-pollen extract, and their possible identity with the active fractions of Kveim antigen

Dr **W J WILLIAMS** (Cardiff) outlined his painstaking endeavours to identify the chemical composition of the inclusion bodies in beryllium disease and concluded that it was probably calcium carbonate Dr **I B SNEDDON** (Sheffield) related his experience of a beryllium skin-patch test. It was similar to the Kveim test in that a sarcoid granuloma appeared, within a month, at the site of application of beryllium, it was specific for berylliosis

Prof **C E DENT** emphasised the value of an oral cortisone test for differentiating hypercalcæmia due to sarcoidosis from that due to a parathyroid tumour in the occasional difficult problem case Whereas cortisone did not influence the serum-calcium level in the presence of a parathyroid tumour, it produced increased fæcal excretion and a fall to normal of the serum-calcium level in sarcoidosis

Dr **S LOFGREN** (Stockholm), who pioneered the view that erythema nodosum and bilateral hilar lymphadenopathy are early manifestations of sarcoidosis, described his experience of this syndrome in Sweden and also the results of renal biopsies in patients with hypercalcæmia due to sarcoidosis In his experience, serum-uric-acid levels were higher in patients with sarcoidosis than in those with tuberculosis or in other control subjects Calciferol provoked elevation of serum-uric-acid as well as serum-calcium levels

Dr **H LUNDBACK** (Stockholm) had studied sarcoid tissue in culture and illustrated his communication with beautiful photomicrographs Dr **CUMMINGS** drew attention to similar studies by his colleague, Dr H Bernton It was hoped that such studies would yield ætiological information or alternatively provide a system for reproducible immunological experiments

Dr **CLIFFORD HOYLE** based his prognosis of the various manifestations of the disease on the course which he had personally followed for many years in a large series of patients He emphasised the high rate of spontaneous clearing of bilateral hilar lymphadenopathy Dr **M SONES** (Philadephia) had followed the course of 200 patients for twenty years There was a mortality-rate of about 10%, mainly from pulmonary heart-disease

Dr **H ISRAEL** (Philadelphia), who had collaborated with Dr Sones in this long-term follow-up, felt that the pattern of disease in their Coloured patients was basically similar to that observed in White Europeans One notable difference was the comparative rarity of erythema nodosum in America

Dr **D G JAMES** outlined the indications for corticosteroid therapy in sarcoidosis, stressing eye disease, disfiguring skin lesions, hypercalcæmia, and a worsening chest radiograph as the most important Yardsticks for measuring the response were clinical, histological, and radiological Steroids were the only drugs which favourably influenced all three By these criteria, triamcinolone was proving just as effective as prednisolone, and a new drug SQ 9727 (Squibb) showed equal promise Mr **R P CRICK** emphasised the value of early corticosteroid therapy for the ocular lesions Dr **INGRID GILG** (Copenhagen) claimed good results from the use of calciferol in patients with cutaneous sarcoidosis attending the Finsen Institute Prof **K WURM** (Freiberg) had observed spontaneous improvement in 16 of 18 pregnant patients He had never seen deterioration during pregnancy, although some relapses had occurred after parturition

During the conference, Dr **K CITRON** and Dr Scadding exhibited the results of their investigations of immunological responses in sarcoidosis

In England Now

A Running Commentary by Peripatetic Correspondents

MORE excitement in Cockaignshire, where Dr. X. has again been hauled before the Executive Committee on a charge of over-prescribing. It seems he was called to a gipsy girl who lived on a barge which, said Dr. X., like a burnish'd throne, burn'd on the water, the poop was beaten gold, purple the sails, and so perfumed that the winds were love-sick. (Here the Chairman over-ruled Mr. Crumb, the Ministry of Health's representative, who remarked that according to his notes, the winds were N.N.E. and blowing a half-gale.) His patient, resumed Dr. X., had been advised that if her nose had been shorter, the whole history of the world would have been different, and she now requested a plastic operation on the N.H.S. in a gallant attempt to improve the situation before it was too late. She agreed with the doctor that she had rather left things until the last moment, but said she had been convalescing from a nasty asp-bite.

The nobility of this *amende honorable* by a beautiful refugee of royal blood had so moved him (declared Dr. X.) that he had unhesitatingly continued the treatment ordered by the lady's previous doctors, viz.:

R Orient pearls *ii*
Vini ad ℥ ½
F. Sol., Sig. ℥ ½ t.d.s., p.c.

Unfortunately the only solvent for Orient pearls, apart from battery-acid, appeared to be 'Zippo' vitaminised port-type tonic wine. This fluid, he claimed, should therefore be regarded in this case as a medicine. How *could* he, he asked (opening the door to admit two workmen carrying a roll of carpet), how *could* he disappoint this brave little woman? Her offer was sublime, a veritable widow's mite, and she had insisted in attending there today although her poverty was such that, as they would see, she had literally nothing to wear except the carpet she was rolled up in. This revelation disturbed the committee considerably.

Mr. Crumb, on behalf of the Ministry, said that the female nevertheless appeared to be adequately nourished and could he assume that the figures 36-24-36 he had just been given were her N.H.I. number? Dr. X. (said Mr. Crumb) had referred them to Herodotus, Plutarch, and certain insolvent Elizabethan playwrights, but what were they compared with Statutory Instrument 1234 M.H., E.C.S. (M.) 4a/36/48? Also (continued Mr. Crumb) the cost to the country of Dr. X's prescription was £1200 for one week's course of Orient pearls, plus 3*s.* 9*d.* for the zippo tonic wine. Admittedly there was 2*d.* back on the bottle, and the Ministry would never condone any N.H.S. patient being deprived of any necessary medicament, no matter how costly, but he had been advised that nitric acid (fuming) was quite as effective a pearl-solvent as zippo, and was equally palatable. The prescription of zippo in this case was extravagance and he asked that 3*s.* 9*d.* be deducted from Dr. X's next cheque, and, while again emphasising that the Ministry would never condone, &c., &c., he recommended that Dr. X. be also fined £1200 for over-prescribing.

* * *

A little charm, she maintained, is worth a lot of knowledge, even in examinations. At the sight of her the most hardened and cantankerous patient would announce that the lump in his neck was a carcinoma of thyroid treated with radio-iodine, or that he had fibrosis of the left upper lobe, "and don't forget to say I have deviation of the trachea." The ladies were equally obliging and whispered words of encouragement and helpful information. "The tall one always asks about me big toe, and 'e wants yer to say 'Gout, which is rare in a woman of this age.' I'm not supposed to say, but I like your face."

But the fortune in her face was not infallible. The last examination she ever intended to take arrived before her social engagements had allowed her time to read the section entitled Neurology. In spite of appealing glances and powerful silent prayers she was led past a coughing patient whom she had met in a previous examination and whose acquaintance she would have been delighted to renew, and was left with an unpromising character who was obviously neurological. Her opening gambit, a bright "What's the matter with you?" received the sullen reply "That's *your* guess." A few ineffective taps with a patella hammer and a jab or two with a pin brought into her mind, as though by divine inspiration, the word syringomyelia, a condition which she had heard was common in examinations but about which she knew nothing.

"Have you got syringomyelia?"

"That's *your* guess."

It was hopeless, and time was passing. She looked round. The examiner was out of earshot. She jabbed again with the pin and said fiercely: "I don't believe you have syringomyelia. I think you have syphilis."

This provoked the desired response. The patient, in high dudgeon, announced that he most certainly had not got syphilis, and that he had syringomyelia, which he could prove because he had dissociated anæsthesia on both sides of the body, &c., &c. He knew all the answers, and so, at the end of five minutes, did she.

She presented the case flawlessly. But rough justice was done. The examiner, equally impervious to her undoubted charms, while agreeing with her diagnosis and physical signs, felt unable to pass her because of her complete inability to describe any form of syphilis that might be considered as a differential diagnosis.

* * *

In appearance and habits we are in no way remarkable, and it has been our ambition to proceed inoffensively through life, breathing quietly through our nose and causing as little fuss as possible. But recent events have conspired to present us to the world as a wrecker, a vandal, a despoiler of other men's property. We are having Plastic Trouble.

The first manifestation of our Trouble occurred while we were on holiday in Devon. We were sitting comfortably one morning on the black plastic seat, placidly admiring the black bath and the lurid murals of orange flames, when we were startled to hear a sharp crack and to have our equilibrium momentarily disturbed. When we looked, what should we find but a comminuted fracture of the left posterior quadrant of the seat. They were very pleasant about it, but we said no, it was entirely our fault, and we must insist on paying (thirty-five bob it cost us, too).

The second manifestation was a couple of months ago, while we were visiting a friend of ours in the pathology department. A nice white job it was, but white or black is all the same to our Trouble, so long as it is plastic, and crack it went just like the first. On this occasion we were slightly less inclined to take an altruistic stand on the matter of payment, but fortunately our friend made little of the occurrence, and we wrote it off to departmental maintenance.

The third attack took place last week, in the newly opened establishment in connection with our hospital library. This time we did not hesitate. As soon as we heard the now familiar crack we made haste to sneak out as unobtrusively as possible, leaving our senior assistant surgeon, the only other occupant of the library, to take the blame.

We find all this very disturbing, and the thought that at any time we must expect to hear the short sharp report marking the end of number four is interfering with our sleep. We had no difficulties of this kind in our youth. We remember a large wooden throne on which we were wont to spend many happy hours singing to the illustrated papers which were stored in lockers on each side of the business portion of the machine. At school the seats were made of inch-thick timber, and in later years we had occasion to patronise a cold stone contraption in a Scottish castle. A man could relax, without fear of personal injury or financial embarrassment, when seats were solid affairs made of natural material and not flimsy wafer-like contrivances whipped up out of coal and air and casein.

Letters to the Editor

CHILDREN IN HOSPITAL

SIR,—I am so fully in agreement with your leading article last week, "What Hospitals for Children ?", that on reading it I felt as if I had written it myself Your recommendations, and those of Professor Illingworth for the care of children in hospital, are nearly all standard practice at Queen Mary's, a general children's hospital of 550 beds of which I have been physician-superintendent since 1953, and we could indeed add to these recommendations from our experience here I am also well aware from personal experience of the difficulty of working to these high standards for children in a small children's ward of a general hospital, or in a purely long-stay children's hospital

While your editorial was in the press, we were informed by the South West Metropolitan Regional Hospital Board, out of the blue and without consultation, that they proposed to close Queen Mary's Hospital for Children, Carshalton, Surrey, within the next few months, and to use the building for another purpose for which they have been unable to secure an allocation of capital from the Ministry of Health.

Before my appointment five years ago I was assured that it was the regional board's intention to develop Queen Mary's fully as a general children's hospital Since then great strides have been made, and the hospital is now fully staffed and equipped to deal with all types of case at all ages from 0 to 16 Queen Mary's has at present 550 beds, with a further 150 in reserve Although more than half the beds are occupied by long-stay cases, 82% of the *children* discharged have been in hospital for less than two months

The board have always worried about the financial implications of Queen Mary's being filled to less than capacity, but they have never shown any serious interest in, or appreciation of, the fundamental problem of children's bed distribution with which your editorial deals

There is no member of the board or of the board's staff who is competent to advise the board on matters of pædiatric planning There is no pædiatric adviser There is no pædiatric committee When a year or two ago I asked if the board would consider seeking expert advice on certain of their pædiatric problems, the Chairman's answer was "No" It seems most unlikely therefore that the board have on this occasion been expertly advised before concurring with the Ministry's suggestion of abandoning, for the sake of temporary financial convenience, the largest general children's hospital in southern England I very *much doubt* whether the Ministry themselves took expert advice before pressing this recommendation, with financial strings attached, on the regional board

I am not one of those who think that it is the board's policy to abandon children's hospitals in favour of small children's wards in general hospitals I would make a graver charge It is that neither the board nor the Ministry of Health have any policy at all on the subject, and do not consider the question of very great importance This is certainly the impression which I have gained after five years as physician-superintendent of the board's only large children's hospital

I have long made plain to the board my view that if they decided to close small children's wards in general hospitals near Queen Mary's, to close children's fever beds, and to prohibit wherever possible the treatment of children in adult wards, the continuation of Queen Mary's as a 550–700-bedded children's hospital would be justified in even cold financial terms and you have already cogently argued in your editorial how much this would mean in terms of improvement of the service given to the children concerned. I do not think that the regional board have taken any serious steps to obtain the facts and figures on which alone an accurate assessment of this possibility could be made This is, in any case, only the most obvious of several ways in which the continuity of the work of this great children's hospital (which deals with 4300 inpatients, 11,500 outpatients, and 2400 surgical operations per annum) could be secured There is not the space here to refer to the implications of this policy on the training of general nurses, which, however, I have recently discussed elsewhere [1]

This decision does not of course affect Queen Mary's alone It is a direct threat to the continuation of the Register of Sick Children's Nurses (Queen Mary's Nursing Training School provides 15% of the annual entry to this register), it would constitute a strong precedent for a reversal of the policy which you advocate in your editorial, and it would make it impossible for the education authority to implement the Minister of Education's recent recommendation about education in hospitals, for most of the children in the South West Metropolitan area

I find it hard to believe that the Ministry and regional board realise just what it is that they are proposing to throw overboard In its combination of acute medical and surgical services with all the special provision necessary in special units for the treatment of poliomyelitis, rheumatism, cerebral palsy, muscular dystrophy, and fevers, and with its hospital school staffed by 40 general and specialist teachers, Queen Mary's provides a better cross-section of pædiatric care than is available anywhere else in the country This is well recognised by the matrons who subsequently employ nurses trained at Queen Mary's, by the medical schools of Guy's and St Thomas's Hospitals, whose one week of residence for an intensive course at Queen Mary's is recognised as important, and is highly valued by the students, and by the Surrey Education Authority who well recognise that it is only in a combined acute and long-stay hospital of this kind that they can efficiently give the services which are expected of them in the education of sick children

I do not at the moment know exactly what form our swift response will take, but I do not believe that this far-reaching proposal, taken, as I believe, without any real understanding of its effect upon the care of sick children, or of the future of pædiatrics or pædiatric nursing, will be allowed to stand

Queen Mary's Hospital for Children,
Carshalton, Surrey

DAVID LAWSON
Physician-Superintendent

SIR,—A warm and sincere welcome to Professor Illingworth's article and your leader of July 26 I agree with almost everything that is said, except at one point where Professor Illingworth does not go far enough He commends daily visiting, which, to me, is as archaic as no visiting at all In my view—and I speak with nearly ten years' experience—unrestricted visiting solves most of the problems of children in hospital

I can best make clear what I mean by unrestricted visiting by quoting from the pamphlet we give to parents It states "You may visit when you like, as often as you like and you may stay as long as you like" We accept any adult visitor and, with supervision, children as well

As there is no limit on length of visit, we are prepared to and frequently do provide residential accommodation for the parents I stress the plural, since it is usually the mother who is admitted with the child, but in certain cases, usually bulbar poliomyelitis in older children, both parents may want to live in the hospital for several days In the matter of admitting parents we do not specifically consider the age of the child, and the only judges of whether they live in or not are the parents themselves

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[1] The Future of Children's Hospitals, *Health Horizons*, summer edition, 1958

Recently we have made a tentative advance from this position, and are trying out the idea of admitting not only the child and its mother, but her other young children as well, for let it be remembered that when a mother comes into hospital with one child, others left at home are deprived of her presence

What we claim for our system is its extreme flexibility, for, as Professor Illingworth points out, the reaction of children (and one might add parents) varies greatly where admission to hospital is concerned Obviously, if the facilities we provide were abused, chaos would result, but I would point out that parents are not the congenital idiots that is sometimes supposed Moreover, hospitals are run for the benefit of the population and not for the convenience of the medical and nursing staffs, and as far as the former is compatible with efficiency it must take precedence over the latter Our experience shows that the more consideration we show for parents' requirements the more consideration they show for us I have by no means achieved all that I should like in this direction, but our modest advance has convinced all concerned that nothing but good has come out of it

May I make a plea that daily visiting is not a target to be aimed at but something to be discarded as insufficient for its purpose

Tunbridge Wells N M JACOBY

SIR,—I should like to make two comments on the excellent and understanding article by Professor Illingworth and the leader in the same issue

First, Professor Illingworth appears to lay inadequate stress on the fact that nearly all children, and certainly those over 6–7 years of age, will be immensely reassured by some logical explanation in simple terms, preferably by a doctor, of the reasons for their stay in hospital As patient and doctor come to know each other better, it is possible and profitable to discuss the problems more fully, to give reasons for the treatment applied, and for the length of stay in hospital The child's understanding of these problems and their discussion is almost always underestimated

Second, your leader, in essence, contains a plea for the centralisation of pædiatric care—for all the very good reasons given However, while this may be practicable in urban areas, it is much less possible in many regional hospital areas because of the enormously increased difficulty of parental visiting with the longer journeys to be made Surely Professor Illingworth's admirable plans for the segregation of all children into their own wards in community hospitals should be followed by a period of reassessment and careful thought before segregation into regional pædiatric hospitals "A relatively small number of big pædiatric hospitals" "in each region" might well cause surprisingly great hardships in visiting

East Grinstead, Sussex RUSSELL M DAVIES

SHOCK

SIR,—Discussions on shock tend to be somewhat kaleidoscopic, each successive view being coloured by the particular interests and experience of its contributor The impression received by the student is necessarily confused, and lacks definition The following is an attempt to define shock in simple terms

The primary function of the blood is to carry oxygen to all parts of the body To this end we are provided with a pump which drives ten pints of blood through an elaborate system of pipes at an appropriate pressure An abrupt fall in this pressure is called shock Shock is acute hypotension This definition has the virtue of impressing on nurses the importance of blood-pressure readings, it covers every conceivable kind of shock, and it has the additional merit of being completely true

The pressure can be lowered in three ways and in three ways only

(1) By weak action of the pump (e g, coronary occlusion, injection of thiopentone, or emotional impact)

(2) By diminishing the blood-volume (i e, loss of blood, plasma, or electrolytes)

(3) By increasing the diameter of the pipes (e g, the vasodilatation which follows an adrenal crisis, the induction of hypotensive anæsthesia, or the development of profound toxæmia)

The clinical features of types 1 and 2 are almost identical, and are associated with compensatory vasoconstriction This vasoconstriction is a mixed blessing It makes the patient look distinctly poorly, and is thus an aid to diagnosis It makes him feel cold, and led us, not so long ago, to warm him up with blankets, hot-water bottles, and paraffin stoves—which is clearly absurd It may still tempt us into operating on patients who have lost a great deal of blood without, as yet, becoming shocked They *will* become shocked if we operate on them

The clinical features of type 3 are entirely different, and rather deceptive The patients are not very pale, but they are slightly cyanosed, the temperature may be raised, and the skin is warm Diagnosis, with a sphygmomanometer, is quite easy—provided one remembers to use the sphygmomanometer

Many cases of diffuse peritonitis combine the features of types 2 and 3, the fluid loss competing with the toxæmic vasodilatation

The treatment of shock is an essay in reason We give blood to the wounded, plasma to the scalded, and electrolytes to those with vomiting, diarrhœa, or an intestinal fistula We give cortisone and noradrenaline to patients with adrenal crises, and to those with diffuse peritonitis we give noradrenaline, cortisone, and electrolytes We have not yet found a remedy for the stricken heart, so to patients with coronary occlusion we give our sympathy

Shock will become irreversible if the blood fails in its primary object of bringing sufficient oxygen to the tissues This will occur if the anæsthetist fails to oxygenate his hypotensive patient, if the traumatic surgeon delays replacement transfusion until the constricted arterioles have strangled the tissues in their grip, or if the peritonitis is so severe and unresponsive to treatment that the poisoned blood-vessels can no longer be constricted by vasopressor agents

Lastly, sweating is an inconstant phenomenon of no diagnostic value Anyone who has danced a Paul Jones will concede the observation that some people sweat—and some don't

South Mimms,
Hertfordshire V J DOWNIE

INTRAVASCULAR CLOTTING IN EXPERIMENTAL HÆMORRHAGIC SHOCK

SIR,—In 85 New Zealand rabbits significant changes in many clotting factors and in the overall blood-clotting mechanisms followed the removal of blood (40 ml per kg body-weight) rapid enough to induce reversible shock The phenomena observed could be divided in three major phases

During and in the first half-hour following hæmorrhage (*early phase*) the plasma-fibrinogen level, the serum-complement titre, and the labile-factor (factor-V) activity dropped rapidly On the other hand, the number of platelets doubled and the speed of formation and the total yield of plasma-thromboplastin were increased The latter finding was apparently due to the development of a potent accelerator of clotting, since the addition of serum from the animal in shock to a system in vitro containing normal platelets and normal plasma resulted in a much more rapid formation and increased yield of plasma-thromboplastin than when normal serum was used Also an experiment in vivo was devised in which normal rabbits received homologous thrombin-free serum from 50 ml of blood Only minor acceleration in the formation of plasma-thromboplastin followed when the serum was from normal animals The injection of serum from animals in hæmorrhagic shock, on the other hand, induced more rapid and complete formation of thromboplastin

As the shock deepened, even after arrest of bleeding and for as long as twelve to twenty-four hours afterwards, different findings developed (*late phase*) While the fibrinogen level continued to drop, platelets also became drastically reduced and the formation of thromboplastin was slow and incomplete

This phase was followed by a *period of recovery*, of two to three days' duration, during which all factors returned to normal. Histologic sections taken between the third and the seventy-second hour showed deposition of material with the morphological and staining properties of fibrin into some of the venous vessels of the lung, kidney, and liver

Analytical study of the fibrinolytic system suggested activation in vivo in the early phase because of considerable increase in the titre of antifibrinolysin and sharp decrease in the activity of profibrinolysin possibly consumed in vivo In the later phase, on the other hand, the serum profibrinolytic activity rose and that of antifibrinolysin decreased, suggesting a return of the fibrinolytic mechanism to normal

Splenectomy within three weeks before hæmorrhagic shock prevented most of the changes described or reduced their severity No clot accelerator developed in the splenectomised animals during the early phases of shock

Thus, significant intravascular clotting occurs in the early phase of hæmorrhagic shock. This statement is based on the findings of accelerated formation of thromboplastin because of the development of a clotting accelerator agent, appearance of thrombocytopenia, intravascular deposition of fibrin demonstrable by histologic techniques, and activation of the fibrinolytic mechanism Since changes were minor in splenectomised animals, the splenic contraction which accompanies severe hæmorrhage may initiate intravascular clotting through the immission into the blood-stream of tissular thromboplastin or of thromboplastic material from the platelets lysed within the splenic sinusoids

These results may have significant applications to human pathology A severe bleeding tendency characterised by fibrinogenopenia, thrombocytopenia, and exalted fibrinolysis has been observed during massive surgical bleeding [1] Earlier work suggested that the hæmostatic breakdown may be due in part to intravascular clotting The results of the present work support this hypothesis

Our investigation was supported by a grant-in-aid from the American Heart Association Essentially similar (unpublished) findings have been obtained in dogs at this laboratory by Leo Gagliardi, Hector Marin, and Mario Stefanini

Joseph Stanton Memorial Laboratories,
Saint Elizabeth's Hospital,
Boston, Massachusetts, U S.A

MARIO STEFANINI
RINALDO A TURPINI

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—May I suggest that much of the difference of opinion expressed in this correspondence is due to failure to distinguish the fundamental differences between a normal disc and a pathological one

The " disc material " one removes at operation, either for " disc prolapse " or " disc degeneration ", has physical properties entirely different from those of a normal disc. It is very similar to the abnormal disc material found in proximity to an early subepiphyseal tuberculous focus—i e., it is solid " stringy " material, aptly described as " crab meat " A normal nucleus pulposus is, of course, fluid—usually under considerable pressure If one compresses longitudinally two normal vertebræ and the intermediate disc, the bone collapses before the annulus ruptures Prolapse of a normal disc either never or hardly ever occurs It is only when the nucleus pulposus has lost its normal characteristics—probably through poor nutrition subsequent to ischæmia, secondary to infection or trauma—that prolapse of disc material takes place Examination of such material does not tell one the properties of normal nuclear fluid

Robert Jones and Agnes Hunt
Orthopædic Hospital,
Oswestry, Salop

ROBERT ROAF

AUTO-ANTIBODIES IN THYROID CARCINOMA

SIR,—The letter by Dr Stuart and Dr Allan (July 5), reporting the presence of high-titre thyroid auto-antibodies in 3 out of 6 cases of carcinoma of the thyroid, raises an important issue if serological tests are to be more widely used as an aid in the differential diagnosis between Hashimoto's disease and thyroid cancer Our experience in this connection may therefore be of interest

Thanks to the cooperation of Prof D Waldron Smithers and Dr N Howard, of the Royal Marsden Hospital, Mr B Truscott, of Addenbrooke's Hospital, Mr A S Till, of the Radcliffe Infirmary, and several others, and by studying patients in the Middlesex Hospital, we have been able to investigate serologically 36 cases of proved thyroid malignancy The sera were tested by the passive hæmagglutination of tanned cells coated with purified thyroglobulin, by complement fixation against thyrotoxic thyroid extract,[1] and by the precipitin reaction in agar The results are shown in fig 1 Auto-antibodies were found in 10 of the 36 cancer patients, the tanned-cell titres did not exceed 25,000 in our series and we have not so far obtained precipitins in a patient with thyroid cancer Only 4 of the 36 patients had complement-fixing antibodies

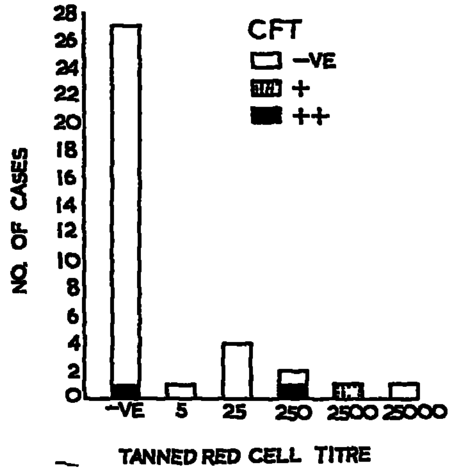

Fig 1—Thyroid auto-antibodies in cancer of the thyroid Tanned-cell hæmagglutination titres are expressed as the reciprocal of the highest serum dilution giving a one + agglutination. A single pipette was used for the serial dilutions of serum Complement fixation (CFT): +, complete inhibition of hæmolysis at serum dilution of 1/5, ++, complete inhibition of hæmolysis at dilution of 1/20 or higher

Of 44 cases of histologically proved Hashimoto's disease examined by the same series of tests (fig 2), all but 2 patients had circulating thyroid antibodies and 28 had levels sufficiently high to give precipitins Complement fixation was positive in all but 6 cases.

The presence of antibodies in the cancer cases probably reflects lymphadenoid changes surrounding the tumour, a known histological feature One would expect to find a high level of circulating antibodies where cancer is associated with widespread thyroiditis, as in the cases reported by Dr Stuart and Dr Allan In such cases, however, clinical features and other thyroid investigations often reveal the presence of a tumour In many cases the character of the swelling or the presence of secondary glands make the diagnosis obvious, while topographical survey of the ^{131}I uptake over the thyroid shows deficient or absent pick-up over the majority of malignant nodules Most Hashimoto goitres involve the entire gland, even when one lobe is larger than the other, and the iodine uptake is greater on the side of maximum swelling The B M R and serum-cholesterol may be of help since hypothyroidism is very uncommon in thyroid cancer and frequent in lymphadenoid goitre The rapid regression of Hashimoto goitres under thyroid medication is another feature of diagnostic value

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[1] Stefanini, M *Proceedings of the VIIth congress of the International Society*, p 78 Basle, 1956

[1] Trotter, W R., Belyavin, G, Wadhams, A. *Proc. R. Soc Med* 1957, 50, 961

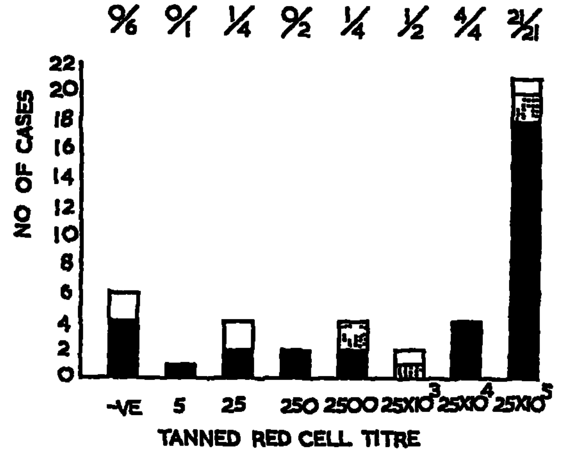

Fig 2—Thyroid auto-antibodies in histologically proved Hashimoto's disease Tests done before or within 3 weeks of operation Results are expressed as in fig 1 The proportion of patients having positive precipitins is shown above the appropriate column

We agree with Dr Stuart and Dr Allan that serological tests should be interpreted only in conjunction with careful clinical assessment and other available investigations, but only a more extensive study of goitre patients, especially those undergoing thyroidectomy, will show whether a differential diagnosis can be made with confidence on the basis of these combined criteria

	DEBORAH DONIACH
The Middlesex Hospital, London, W 1	I M ROITT R VAUGHAN HUDSON

ARTIFICIAL RESPIRATION

SIR,—In your annotation on this subject[1] you say

" *Even with intubation Safar et al did not succeed in moving more than 700–260 c.cm of air with either the Holger-Nielsen or the Silvester method This is far below the ventilation regularly attained in the investigation of Gordon et al, but the reason for this difference is not clear* "

When a tracheal tube was in place, we moved with the Holger-Nielsen method in 5 curarised subjects tidal volumes of 260–840 c.cm (average 655 c cm)—the small tidal volumes in obese subjects, the large tidal volumes in lean subjects Our subjects were lying on a hard table Gordon moved approximately 1000 c cm per breath in tall, lean, and healthy volunteers, who were lying on the floor Our small tidal volumes are easily explained by the reduced chest distensibility, since some of our subjects were heavy and short Our large tidal volumes are smaller than Gordon's because our subjects were lying on a table The small tidal volumes are not surprising in view of the findings of other investigators—namely Nims et al,[2] Waters and Bennett[3]—who could move only 140–280 c cm per breath with these push-pull methods and with a tracheal tube in place, they studied apnœic patients who were obese or whose lung-chest distensibility was reduced by disease

Without tracheal tube 11 of 15 subjects (lying on the floor) could not be ventilated with the Holger-Nielsen method, because of upper airway obstruction This was confirmed recently by Gordon et al,[4] who were unable to ventilate 40–50% of the curarised subjects studied when they did not use a tracheal tube

We learned from a separate study of unconscious patients who were not curarised that pharyngeal obstruction by the tongue due to flexion of the neck and sagging of the mandible is at least as common in the prone as in the supine position, even when an artificial oropharyngeal airway is in place The Esmarch-Heiberg manœuvre (extension of the neck plus forward displacement of the mandible) seems to be the single most important point in respiratory resuscitation

You remark on successes known to have followed use of the Holger-Nielsen and Silvester methods But who knows whether an asphyxia victim in the field survives in spite of or because of the method applied? Many comatose asphyxiated patients have been awakened by external stimuli only Airway obstruction is unpredictable There is no doubt that occasionally the airway is open during performance of the push-pull methods, but the rescuer is unable to recognise movement of air while working on the patient's chest

You suggest that dizziness may affect the operator while performing mouth-to-mouth breathing We confirmed Elam's data[5]

The rescuer could perform mouth-to-mouth breathing for 30 minutes or longer without becoming dizzy Whenever he felt dizzy he automatically reduced the rate of inflations, and levelled off at an end-expiratory carbon-dioxide level of 3–4%, while that of the subject was 4–5% The oxygen saturation and the end-expiratory carbon-dioxide level in the subject were maintained at normal levels with tidal volumes at least twice as large as normal at a rate of 10 inflations per minute or more The restricting factor in prolonged mouth-to-mouth breathing is not dizziness of the operator, but fatigue of his back and hands

A motion picture on *Respiratory Resuscitation Techniques*, which was made during one of our experiments, shows the experimental techniques and results better than a paper The motion picture may be borrowed from Army Medical Institute of Research, MAVD, Walter Reed Hospital, Washington, D C (Attention Sergeant H Dixon)

Baltimore City Hospitals, Baltimore, Maryland	PETER SAFAR Chief, Department of Anesthesiology

OOPHORECTOMY AND BREAST CANCER

SIR,—Your leader of July 12 refers in passing to the variable persistence of œstrogen excretion following bilateral oophorectomy and adrenalectomy for breast cancer

I think it worth calling attention to a simple and practical possibility that may repay exploration, before some mysterious third source of œstrogens is postulated or sought—namely, the ovarian hilus cells These (which resemble Leydig cells and are invariably present) are found throughout the mesovarium, and extend medially along the ovarian ligament. The recent monograph of Morris and Scully[1] gives an account of them together with evidence that they can produce œstrogen; an earlier review is that of Sternberg.[2]

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[1] *Lancet*, 1958, i, 1322.

[2] Nims, R. G Conner E H, Botelho, S Y, Comroe, J H, Jr *J appl Physiol* 1951, 4, 486

[3] Waters, R M, Bennett, J H *Anesth Analg* 1936 15, 151

[4] Gordon, A S, Frye, C W, Gittelson, L, Sadove, M S, Beattie, E J, Jr *J Amer med Ass* 1958, 167, 320

[5] Elam, J O, Brown, E S, Elder, J D, Jr *New Engl J Med* 1954, 250, 749

Experience shows that oophorectomies for breast cancer vary: sometimes the operator seems bent on removing nothing whatever except the ovary, whilst at other times a generous slice of mesovarium is included. This may account for the variations noted. It seems clear that as much mesovarium and ovarian ligament as possible ought to be removed, and a tentative case might be made for bilateral removal of the adnexa.

London, W.C.1 P. E. HUGHESDON

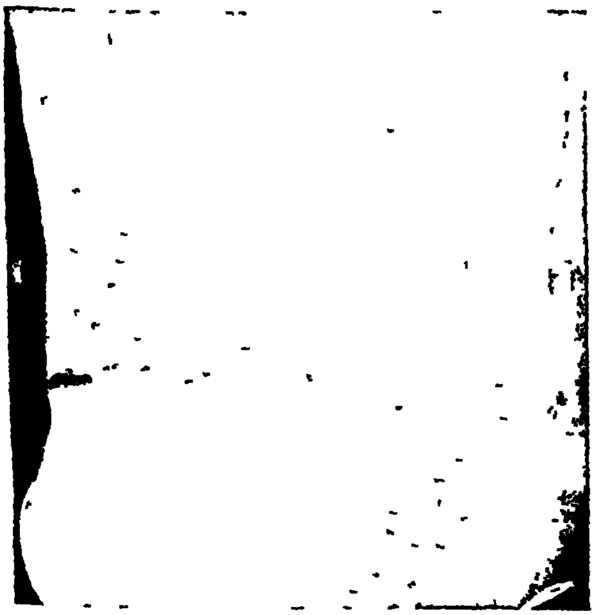
SKIN REACTION INHIBITED BY X-RAY THERAPY

SIR,—The following case is reported in the hope that some useful explanation may be obtained.

A man, aged 63 years, was admitted with a history of four months' pain in the left buttock. X-ray examination showed a large osteolytic lesion in the right ilium, which was diagnosed as a secondary deposit from a carcinoma of the prostate. The gland was enlarged, hard and irregular. The patient complained of moderately severe pain in the buttock three minutes after the intravenous injection of 250 mg. of stilbœstrol diphosphate ('Honvan'). There were no other positive findings.

On April 14, 1958, he started on a palliative course of deep X-ray therapy (190kV 300r daily skin dose to a field 20 cm. × 15 cm.). He had no treatment on April 19 and 20. On April 21 he awoke with a patchy macular rash on his trunk, thighs, and arms. There were also a few spots on his forearms and legs. The area being treated by X rays was completely clear and showed no evidence of the rash or of radiation erythema. The borders of the treated area were fairly sharply demarcated; if anything, the unaffected region tended to spread outside the blue lines used to delineate the area for treatment. Owing to the curvature of the buttock some of the radiation was likely to fall outside the prescribed rectangle, particularly at its medial and lateral sides.

The accompanying photograph was taken on April 22, by which time there was a faint suggestion of erythema in the irradiated area but certainly no blotchy rash. The patient was then given antihistamine drugs, and the X-ray therapy continued. The rash disappeared the next day. The cause of the rash is unknown. Perhaps it was due to an aspirin tablet he took the day before, perhaps to an enema.



A presumably allergic reaction seems to have been inhibited by a dose of 1500r in five days, and this inhibition occurred before any skin response to irradiation could be seen.

St. Luke's Hospital,
Dublin JOHN B. HEALY

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[1] Morris, J. McL., Scully, R. E. Endocrine Pathology of the Ovary, chapters 2 and 6. London, 1958.

[2] Sternberg, W. H. *Amer. J. Path.* 1949, 25, 493.

SHOULD BIBLIOGRAPHIES GIVE TITLES OF PAPERS?

SIR,—I should like to add my plea to Mr. Patey's (July 19) that bibliographies should include titles of papers. This is particularly important in review articles.[1] The references are quoted with more care, the bibliography itself makes interesting reading. These and other advantages easily compensate for the exclusion of a short article.

With too much to read, I value quality before quantity.

Medical Unit,
The Royal Infirmary,
Cardiff PAUL FOURMAN

NON-ADRENAL FEMALE PSEUDO-HERMAPHRODITISM ASSOCIATED WITH HORMONE ADMINISTRATION IN PREGNANCY

SIR,—Attention has recently been drawn to the occurrence of partial virilism in female infants when the mother has received hormonal treatment during the pregnancy for repeated miscarriages or hæmorrhage during pregnancy. Lawson Wilkins and his colleagues[2] from the Johns Hopkins Hospital have collected 18 instances of this condition as well as 3 exactly similar in which the mother had received no hormones. Other instances have been reported by Hayles and Nolan[3] and by Nellhaus.[4] Wilkins has made a plea for smaller dosage of steroids and for the deferment of treatment until after the tenth week of pregnancy.

My colleagues and I at The Hospital for Sick Children, Great Ormond Street, have seen 3 such babies in the past year or so. They will be more fully reported elsewhere (with due acknowledgment to all who have contributed), but as the degree of masculinisation appears clearly in these to be related to the intensity and date of starting treatment they are briefly reported here.

CASE 1.—Aged just over three years on admission, this child, registered as a male, had a phallus with a urethral opening beneath it, and a scrotal-like structure with a median raphe but no testicles. Investigations excluded adrenal abnormality, and female sex was indicated by the nuclear chromatin in the white blood-cells. Laparotomy showed a normal uterus, fallopian tubes, and ovaries but absence of a vagina. In view of repeated miscarriages the mother had been given (as soon as she was known to be pregnant) tablets containing ethinylœstradiol 0.01 mg. and methyltestosterone 3 mg. twice daily for one month and three times daily for two months. She also had an implant of progesterone (50 mg.) in the third month and again in the fourth month of pregnancy.

CASE 2.—Aged nine days on admission, this child, of whom the sex had been considered doubtful at birth, showed an enlarged clitoris with a urethral opening on its under surface, and fused labia with a small vaginal orifice. There was no evidence of adrenal abnormality. Female sex was established by the nuclear chromatin of the white blood-cells. Examination under anæsthesia showed a wide vagina and normal cervix.

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[1] Waymouth, C. *Nature, Lond.* 1956, 177, 98.

[2] Wilkins, L., Jones, H. W., Holman, G. H., Stempfel, R. S. *J. clin. Endocrin.* 1958, 18, 559.

[3] Hayles, A. B., Nolan, R. G. *Proc. Mayo Clin.* 1958, 33, 200.

[4] Nellhaus, G. *New Engl. J. Med.* 1958, 258, 935.

From the sixth week of pregnancy the mother had taken six tablets a day containing 0 01 mg of ethinyloestradiol and 10 mg of ethisterone until she was delivered by cæsarean section at the thirty-eighth week

CASE 3 —This child, admitted at the age of four weeks, was noted to have a large clitoris at birth, confirmed on admission Examination showed the presence of a vagina and a small uterus, the ovaries were probably felt There was no evidence of adrenal abnormality and female sex was confirmed by the nuclear chromatin in the white blood-cells The mother had received tablets of methyltestosterone 10 mg three times a day for three weeks about the third month of pregnancy for vaginal bleeding and again at about the sixth month for about six weeks for the same reason Seen at one year of age this child showed a clitoris only slightly larger than normal

These three cases have been set out in order of severity In case 1 the mother received the earliest and most intensive treatment, but even in case 3 the mother was not treated until the third month It may be, as Lawson Wilkins and his colleagues remark, that these children might not have been born at all but for the treatment, but in view of the psychological and other problems presented they appear to support the plea for not starting it too early and keeping the dosage as low as possible

The Hospital for Sick Children,
Great Ormond Street,
London, W C 1

ALAN MONCRIEFF

PS—Since submitting this letter, I have read an annotation in the *British Medical Journal* (July 26, p 218) which suggests postponing hormone treatment until after the fourth month —A M

INTERFERENCE WITH TELEVISION

SIR,—*I happen to live in the vicinity of Harley Street* and to possess a television set The only time I *try* to look in in the afternoon is when show jumping and Wimbledon are on It is quite impossible to ask anyone to share this pleasure with me because some selfish doctor or nursing-home turns on a machine without a suppressor, which, apart from causing a tremendous roar, completely obliterates the picture The Post Office say that they cannot force anyone to add a suppressor (which I believe costs half-a-crown) and that they have more complaints from around here than in any other area

London, W 1

ENID DOUGLAS DERRICK

HÆMOPHILIA-LIKE STATES IN GIRLS

SIR,—Professor Quick and Miss Hussey,[1] when they discuss hæmophilia-like states in girls, have omitted mention of the cases of hæmophilia in human females which occurred in the family originally described by Treves[2] and subsequently by Bulloch and Fildes,[3] by Handley and Nussbrecher,[4] and by myself[5] One does not expect authors to review the whole of the published literature each time they write a case-report, but this family is unique in two ways Firstly, the family studies extend over a very long period, and secondly, this family is probably the first in whom the diagnosis of hæmophilia was established in females with any degree of certainty Quick and Hussey are clearly aware of these reports since they mention them in other publications[6 7]

They have objected to the diagnosis of hæmophilia because of the alleged male-to-male inheritance in the first four generations and also because hæmophilia-like disease was not excluded Their first objection I have already discussed in detail[5] It is no longer possible to prove or disprove this inheritance since the patients all died very many years ago, the history of bleeding in them is very scanty and often amounted to no more than a tradition in the family that they were bleeders The inheritance in recent years is typical of hæmophilia

Their second objection was possible but improbable Blood of hæmophiliacs from 3 different families was used in testing this family It was possible to deduce the fact that at least 2 hæmophiliacs with different clotting-times were used[5], they were consequently probably unrelated The fact that 3 unrelated hæmophiliacs were used did not appear to be important at the time and so was not mentioned These three hæmophiliacs are now known to have classical hæmophilia It would be unlikely that an error in the diagnosis of hæmophilia would have been made in all these cases In any case the matter has been put beyond doubt by the statement of Taylor and Biggs[8] that later work has shown that the family described in my paper have classical hæmophilia

Groote Schuur Hospital,
Cape Town

C MERSKEY

PREVENTION OF POSTOPERATIVE TETANUS

SIR,—Professor Pannett[9] criticised the use of the tourniquet in limb operations, a routine which he regards as a harmful and backward step in surgery He quotes two unjustifiable risks associated with the use of a tourniquet (1) damage to nerves and muscles, and (2) lowering of tissue resistance to infection At the time his letter was published a married woman, aged 39, died in Melbourne from tetanus contracted during an operation of election—namely, a meniscectomy—in which a tourniquet was used This case and its circumstances are pertinent to Professor Pannett's letter and to your editorial comments[10 11] on the importance of efficient ventilation in operating-theatres

The infection was a fulminating one and death occurred three days after a short incubation period of five days *Clostridium tetani* and *Cl sporogenes* were isolated at necropsy, and during life from fluid inside the knee-joint and from the surrounding tissues The sterilisation of the instruments, textiles, dressings, talc, &c, was carried out efficiently with tested equipment The operating-theatre and sterilising annexe were connected by a sliding door which is kept open during the setting-up for an operation and both rooms were ventilated by means of exhaust fans placed in large ducts opening in the ceiling These ducts were protected by a wide-mesh wire guard and could not be cleaned except by unscrewing the guard As might be expected, they were heavily laden with dust Cultures from the dust in each yielded various species of clostridia, including a non-toxigenic strain of *Cl tetani*

When the fan in the sterilising annexe is operating, air is sucked into the theatre through its dust-laden duct or from the corridor, and vice versa When the fans are not operating air currents set up by external wind or by convection pass along the ducts providing a further opportunity for dislodging dust Since the sterilisation was adequate it can only be assumed that this infection developed from dust contamination of the wound or the instruments during the operation To what extent the use of a tourniquet and a tight bandaging of the wound thereafter contributed to tissue anærobiosis is difficult to say However, this case raises several interesting points

In the past five years in Victoria there have been 56 notified cases of tetanus, of which 6 (about 11%) followed operations of election Of these 6 cases, 3 were operations on the knee or ankle joints Sevitt[12] reported 2 hospital-infected cases, both involving operations on the leg, and he also described[13] a case of gas gangrene after an operation on the ankle Of the 4 postoperative tetanus deaths in England and Wales in 1954 2 followed operations on the foot[14] Since such operations must constitute only a small fraction of the total surgical load they seem to carry an unexpectedly high risk of tetanus In contrast to the present trend, Wainwright[15] reported, from a survey of tetanus over twenty years, that, while postoperative tetanus accounted for 10% of civilian cases, 70% followed gynæcological and abdominal operations

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[1] Quick A J Hussey C V *Lancet*, 1958 i, 1294
[2] Treves F *ibid* 1886 ii 533
[3] Bulloch W Fildes P Treasury of Human Inheritance, parts v and vi, p 169 University of London, Francis Galton Laboratory for National Eugenics 1911
[4] Handley R S Nussbrecher A M *Quart J Med* 1935, 4 165
[5] Merskey C *ibid* 1950 20 299
[6] Quick A J Hussey C V *Amer J Dis Child* 1953, 85 699
[7] Quick A J Hemorrhagic Diseases, p 186 London 1957
[8] Taylor K, Biggs, R *Brit med J* 1957, i, 1494
[9] Pannett C A *Lancet* 1958, i, 545
[10] *ibid* 1953 ii 1133
[11] *ibid* 1955 ii 39
[12] Sevitt S *ibid*, 1949, ii, 1075
[13] *ibid* 1953, ii, 1121

Although postoperative tetanus is an uncommon disease, the case-fatality rate is high (about 44% in Australia)[16] In its elimination as a surgical hazard, four levels of prevention, two general and two specific, can be considered

The first is the intelligent use of efficient sterilisation equipment recommended by Bowie,[17] a factor which does not require comment here

The second is concerned with effective ventilation of operating suites using filtered air and a plenum system, based on the principles described by Bourdillon and Colebrook[18] and more recently by Blowers[19]

The third lies in the more conservative use of tourniquets, as suggested by Professor Pannett

The fourth is to immunise patients with tetanus toxoid before all elective operations of the lower limbs in which tourniquets are used, particularly those involving the knee or ankle joint If the patient has not been actively immunised, two injections, one four weeks before and another at the time of operation, would not seriously interfere with the management of a case The individual who has been actively immunised may be given a preoperative booster injection of toxoid In emergency operations of the type being discussed prophylactic antitetanus serum followed by active immunisation during convalescence would be a useful safeguard

While dealing with the subject of selective immunisation in non-traumatic surgery it might be suggested, on the analogy of passive transfer of immunity in diphtheria,[20] that neonatal tetanus, which accounted for 4 9% of cases in an Australian series[16] and 3 4% of deaths from tetanus in England,[21] could be abolished by active immunisation of the mother during pregnancy

Finally, as more individuals are now being actively immunised against tetanus[22] a clear distinction should be drawn *for the patient* between active and passive immunisation We recommend that individuals who are given tetanus toxoid be informed, verbally and perhaps in writing, that the immunisation was a "T T injection" and when antitoxin is used it is always referred to as an "A T S injection"

School of Bacteriology,
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Victoria, Australia

SYDNEY D RUBBO

CHARGES FOR NIGHT CALLS

SIR,—In your leading article of July 5, you described the National Health Service as simply a legislative device by which doctors can continue their work without charging fees, and this was the most attractive part of it to most doctors whether they actually approved of the service or not But after a very short time, the Socialist Government which had sponsored this free service put a charge on drugs and appliances as a deterrent, and I think that was quite wrong The collection of these charges must have caused considerable misgivings to chemists and opticians and others who had to collect this payment from some patients who could ill afford it

Dr Guy Dain, who always expressed himself as being wholeheartedly in favour of a comprehensive medical service available to 100% of the population, has now suggested[1] that "it would probably remove some disgruntlement if the doctor could make a charge (to be fixed) for late and night calls for visits" What amount would Dr Dain suggest, I wonder, as the fee for a late call and for a night call? Is the same fee to be applicable to all classes, irrespective of their income group and irrespective of whether they are old-age pensioners? Is the fee to be retained by the practitioner himself, or will he be merely collecting it on behalf of the Treasury, in view of the fact that this charge, like the charges on prescriptions and appliances, is intended as a deterrent

Many doctors working in the service today have never worked in the times when doctors charged fees to patients, and probably have no desire to do so now I think it would cause considerable embarrassment to a young doctor if he had to demand a fee from a patient who had been taken ill in the night, or even from anxious relatives If, from time to time, additional fees are to be charged to patients in order to deter them from using the National Health Service, it makes a nonsense of the whole scheme, and it would be better to return to the old system where patients made their own arrangements

Camberley

LESLIE HARTLEY

THE DAY HOSPITAL

SIR,—The excellent article by Dr Craft (July 19) on the treatment of depressive illness at the Maudsley Hospital shows a higher rate of recovery in patients treated in the day hospital than those treated in the adjoining inpatient hospital The investigation would have been even more useful, however, if it had been undertaken as a piece of interdisciplinary operational research including the contributions of a sociologist and a cost accountant

Mental illness involves interpersonal relationships at home and at work There is less disturbance of family relationships when the patient still lives at home than when he goes into hospital, and this may well contribute to increased speed of recovery Again, he will probably find it easier to resume work or obtain a new job if he has been attending a day hospital than if he has been an inpatient, but as yet these points have not been compared sociologically

Equally important is the economic aspect of day hospitals, where comparable medical care can be given at a substantially lower cost than in an ordinary hospital It is regrettable that in the most recent Ministry publication on hospital costing there is no breakdown of the comparative costs of care of Maudsley Hospital inpatients and those in the adjoining day hospital The comparison may well be difficult, but this is the type of problem that is dealt with daily by industrial cost accountants

In the years to come, day hospitals will probably have an increasingly important role in the treatment of non-catastrophic illness, and their development may well influence the whole concept of hospital design and medical care in urban areas Such changes can be justified only by comprehensive research which, under present financial conditions, can most easily be undertaken by teaching hospitals, and must include the social and economic needs of the family and of the community

Marlborough Day Hospital,
38 Marlborough Place,
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THOMAS M LING

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[14] *Brit med J* 1957, 594
[15] Wainwright, J M *Arch Surg* 1926, 12, 1062
[16] Johnston, D W *Med J Aust* 1956, i 710
[17] Bowie, J H *Pharm J* 1955, 174, 473, 489
[18] Bourdillon R B, Colebrook, L *Lancet*, 1946, i 561, 601
[19] Blowers, R Symposium on Hospital Coccal Infections, 1957, no 14
[20] Barr, M, Glenny, A T, Randall K J *Lancet*, 1949, ii, 324
[21] Conybeare, E T, Logan W P D *Brit med J* 1951, i 504
[22] Scott, T L *ibid* 1958, i, 1176

[1] *Brit med J* July 5, 1958, suppl p 1

ORAL TREATMENT OF PERNICIOUS ANÆMIA

SIR,—I should like to comment upon some aspects of the challenging article by Dr Heathcote and Dr Mooney[1] They state that they have isolated a vitamin-B_{12}-peptide from a streptomyces fermentation "shown clinically to be the most effective oral preparation yet available" for the treatment of pernicious anæmia The "failure of simple proteolysis in the stomach" to which they refer, seems unlikely to be of ætiological importance in that disease, but a vitamin-B_{12}-peptide might well be physiologically significant in the transport of vitamin B_{12} across the intestinal wall Consequently it is disappointing to find that the authors have submitted no convincing evidence that their vitamin-B_{12}-peptide was more active hæmatopoietically than its content of vitamin B_{12}

Thus, as pointed out by Dr Latner,[2] the high vitamin-B_{12} content alone (100 µg) of the peptide given daily during the initial stage of the therapy of each patient may have produced the remissions noted Failure to relapse thereafter during a few months of reduced maintenance therapy is notoriously poor evidence of therapeutic activity Even if Dr Heathcote and Dr Mooney's claim for the therapeutic efficacy of their vitamin-B_{12}-peptide is accepted, the conclusion that "intrinsic factor does not exist" seems irrelevant

In their reply[3] to Dr Latner's letter, Dr Heathcote and Dr Mooney express lack of confidence in the interpretation of "short-term responses" If by that phrase they refer to carefully controlled observations upon serial reticulocyte responses during successive 10 to 14 day periods of uniform daily therapy in individual patients, it may be of more than historical interest to point out that it was in large part with the aid of such a clinical index that therapeutically effective liver extracts were originally developed and that the clinical activity of vitamin B_{12} itself received final confirmation Indeed, by such methods the activity of the so-called gastric intrinsic factor was first demonstrated Since then its more convenient assay by comparative observations upon the assimilation by individual patients of small single doses of radioactive vitamin B_{12}, first without and then with intrinsic factor, has become an established practice

In my opinion, until such comparisons in the same patient are appropriately applied to the present problem, first employing single doses of not more than 5 µg of vitamin B_{12} alone, the alleged superior hæmatopoietic activity in pernicious anæmia of the vitamin-B_{12}-peptide over that of its content of vitamin B_{12} will remain uncertain

Harvard Medical School,
Cambridge, Massachusetts

W B CASTLE

RECORDS OF IMMUNISATION

SIR,—I am prompted to write by Dr Carson's letter of July 19 If the wear and tear on my Post Office Savings book is any criterion, I hope that Dr Carson's (or are they Burroughs Wellcome's?) cards are made of a highly durable synthetic plastic

Chirk,
North Wales

R P W KUP

RADIOGRAPHERS IN THE N H S

SIR,—Since you wrote on this subject, over a year ago,[4] the shortage of radiographers appears to have increased steadily, with little further mention of the fact in print Medical staff of hospitals where the radiological service is necessarily drastically reduced are naturally asking what is being done and what are the prospects of restoring a proper service

As there is a limit to what can be done by the heroic devotion of radiographers, the understaffed departments are faced with the unavoidable choice of foregoing the less urgent types of examination (and who is to decide which are these?) or of employing unqualified personnel

A somewhat similar situation during the war was met by the Services training their own radiographers to an acceptable minimal standard, and I fear that stark necessity may shortly force some hospitals and chest clinics to train local labour to undertake the simpler radiographic examinations by rule-of-thumb methods Once started, such a practice would be difficult to stop, and it might well lead to degrading of radiographic standards generally unless arranged under the direction of the Society of Radiographers

Understaffed X-ray departments would welcome an authoritative statement about the present and future position of radiography

Ashford Hospital,
Ashford, Middlesex

J A BROCKLEBANK

DURATION OF PREGNANCY

SIR,—The duration of pregnancy, measured in days or lunar months, varies considerably from one "normal" baby to another, and so prediction of the date of birth is subject to error even in normal pregnancies The average length of gestation is accurately known to apply this to an individual case, some correction is required for the "time-scale" of the particular mother and child The late Dr W E Dickes Rost suggested in her unpublished notebooks that the required correction might be made by substituting the length of the mother's periods for the lunar month, as the unit of time It was hoped that calculation of the expected length of pregnancy as ten times the length of the mother's periods would be more accurate than the present system It has already been reported that the incidence of abortion shows peaks at intervals of about 4½ weeks[1]

Department of Anatomy,
University of Sydney,
New South Wales

F W DICKES ROST

FLAMMABLE CLOTHING

SIR,—I can fully appreciate the disappointment expressed by Mr Willby (July 26, p 217), press officer to the British Standards Institution, at the discussion on flammable clothing at the meeting of the British Medical Association in Birmingham, for it is quite possible that many of the speakers confused the B S I with the British Government Many of us who work in burns centres are dissatisfied not so much with the B S I, which does very good work within its very definite limitations, but rather with a Government which, in spite of the recommendations made in the B S I report, has done virtually nothing to popularise the existence of attractive flame-resistant clothing fabrics or to encourage their manufacture and sale at a reasonable price, even though this might require a special, though probably only temporary, Government subsidy, as recommended by Colebrook et al[2]

Experience in South Wales over the past two and a half years has shown that many big departmental stores or shops still refuse to stock flame-resistant fabrics some may have the fabrics in stock, but will not display them because of their high price Even more staggering are the popular misconceptions held by directors, buyers, and departmental managers, let alone the sales staff, about the relative flammability or safety of different fabrics It is thus very distressing to find that a good deal of one's personal effort and that of the various home-safety committees in encouraging parents to ask for flame-resistant fabrics is wasted by apathy or ignorance in the retail trade

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[1] *Lancet*, 1958 i, 982
[2] *ibid* p 1077
[3] *ibid* p 1177
[4] *ibid* 1957, i, 1030

[1] Pearce, T V *Biometrika* 1930, 22, 250
[2] *Brit med J* 1956, i, 1379

Welsh Regional Plastic Surgery,
Burns and Jaw Injuries Centre,
St. Lawrence Hospital, Chepstow

MICHAEL N TEMPEST

NEOLOGOPHILIA

SIR,—To the two (or perhaps three) reasons for learning Greek given by Dean Gaisford we must now add another to allow us to understand the less literate contributions to medical journals Yet I doubt if Bentley himself would have guessed that thalassæmia is not a perfusion with sea water but an inherited abnormality of hæmoglobin The neologopoietic author ought to use his Liddell and Scott with care even a simple word like anæmia meant something different to Homer.

Your own contribution, Sir, to this discussion (July 26, p 215) is regrettable Greesham's Law is as valid in journalism as in finance You may not be guilty of counterfeiting but to put this verbal snide into circulation is a crime just as grave

Hoccombe Bottom,
Somerset

J A BOYCOTT

Parliament

Children's Bill

THIS Bill [1] includes a provision that in considering whether to make an adoption the court shall have regard "to the health of the applicant" At the report stage on July 25 in the House of Commons, to this provision were added the words "as evidenced, in such cases as may be prescribed, by the certificate of a fully registered medical practitioner" Some members regretted that the amendment did not go further and make medical testimony compulsory Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Home Office, gave an assurance that the Lord Chancellor intended to make rules requiring a medical certificate in most cases But he did intend to except some cases, when, for instance, the applicant was the mother of the child

The Bill was read a third time

QUESTION TIME

Suicides and Attempted Suicides

Mr KENNETH ROBINSON asked the Home Secretary if he had yet reached a conclusion on the desirability of amending the law relating to suicide and attempted suicide —Mr R A BUTLER replied No, Sir My study of this question suggests that in its practical aspects the problem is largely one of ensuring that those who need care or treatment to prevent them from endangering themselves or others in fact receive it In general, where this can be done without the intervention of the courts proceedings are not taken, but there is a residue of cases in which the person concerned cannot be given or will not accept, care or treatment without the intervention of the courts I shall continue to study this aspect of the matter and I am in consultation with the Minister of Health

Mr ROBINSON Is not the Minister taking rather a long time to reach a conclusion on a matter where the overwhelming weight of opinion is in the direction of reform? If the Government are not prepared to take the initiative in this matter, can he say what would be their attitude towards the initiative being taken by a private Member?—Mr BUTLER I cannot state what my attitude would be towards the initiative of a private Member until I know the nature of that initiative. I do not know whether the hon Member is aware that the joint committee of the British Medical Association and the Magistrates' Association has commended the law and practice in Scotland in this matter The reason I am not going any further in answer to the hon. Gentleman is that we are at present carefully considering that with a view to seeing what we might do about it

Mr CHARLES ROYLE Will not the Minister hold out a little more hope in this matter, particularly as involved and responsible organisations are taking the view that they are? Cannot we get more in line with other countries who never regard attempted suicide as a criminal matter?—Mr BUTLER It so happens that in 1956, the last year for which I have figures, proceedings were taken in 613 cases of attempted suicide out of a total of over 5000, and only 6 7% of these proceedings resulted in sentences of imprisonment, and there is a certain limit to that But I am considering the whole question

More Dentists

The Ministry of Health, after consultation with the University Grants Committee, have accepted the recommendation of the McNair Committee that the annual output of dental schools in Great Britain needs to be expanded to produce at least 800 dentists who will practise in this country To allow for wastage and students from overseas the schools' present potential intake of about 650 students per annum in their first professional year must be expanded to something over 900 places The Ministers aim to start expansion as soon as possible, and, when considering projects for inclusion in the Government's programme for major hospital building schemes, they will give due regard in consultation with the University Grants Committee, to proposals which will contribute to it.

Working Party on Hospital Medical Staffing

Mr ARTHUR BLENKINSOP asked the Minister of Health how many of the members appointed by himself and the Secretary of State for Scotland to the working party on medical staffing of hospitals had experience of the staffing problems of any other than teaching hospitals —Mr R. THOMPSON replied All 6 2 are currently serving in non-teaching hospitals, the other 4 are concerned in the health departments with the staffing problems of the hospital service as a whole

Smoke Control

The Minister of Housing and Local Government has confirmed 34 orders establishing smoke-control areas 13 orders are under consideration and a further 102 orders have been provisionally notified to him by local authorities

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[1] See *Lancet*, 1958, i, 646

Appointments

COUSTON, T A., M B St And. assistant psychiatrist, St Margaret's Hospital Birmingham

CUST, GEORGE, M.B. Leeds D P H M O H, Cleethorpes and Grimsby

FEE, W M M.B. Edin., D P.H depute M O H and depute port M.O, Greenock

GARDEN R A, M B Glasg school M O, Nottingham

HUNTER, J K., M.B Glasg, D T M & H., D.P H. assistant administrative M O, Eastern Regional Hospital Board, Scotland

TURNER, WILLIAM, M B Leeds D P H senior assistant M O and school M.O., Ilkley, Otley, and Wharfedale, Yorkshire.

East Anglian Regional Hospital Board

BLACK, J H A. M.B Belf registrar in psychiatry, Fulbourn and Addenbrooke's Hospitals

CLARKE, H L, M.B. Lond anæsthetic registrar, Newmarket General Hospital

CRAGGS, D F M B Lond. registrar in psychiatry, Fulbourn and Addenbrooke's Hospitals

MACKENZIE K M M D Lond, M.R.C.P part-time consultant physician, West Suffolk General Hospital

ROBERTS J H, M.B. Lpool radiological registrar, Ipswich and East Suffolk Hospital

Births, Marriages, and Deaths

BIRTHS

SMITH —On July 19, to Kathleen Smith (née Turner), M B., and Irvine Smith F R.C.S, at Burton-on-Trent —Christopher Frederic, a brother for Anne, Dorothy and Geoffrey

SHEMILT —On July 25 at Salisbury Infirmary, Wilts, to Jane (nee Brownscombe), wife of Philip Shemilt, F R.C.S —a daughter

Obituaries

GEORGE MACFEAT WISHART

M D, B Sc Glasg, F R F P S

George Wishart gave Glasgow University forty years of effective and varied service as scientist, teacher, and administrator He retired in 1947 from the chair of applied physiology to preside over the faculty of medicine, and the only flaw in his colleagues' and students' admiration for the dean was regret at the loss of the professor

His father was a Glasgow grain merchant and he was educated at Uddingston Grammar School and the University of Glasgow, where he graduated B SC and M B in 1918 After serving a year with the R A F medical service he returned to the university as an assistant in the institute of physiology Two years later he was appointed to the Grieve lectureship in physiological chemistry He found time for postgraduate study in Sweden and Germany, and, nearer home, he spent several vacations working at the Hannah Dairy Research Institute during its early formative years Much of the research of these early years was summarised in his authoritative M D treatise on basal metabolism, for which he was awarded the Bellahouston medal in 1926, and in his *Groundwork of Biophysics* which was published in 1931

In 1935 Wishart was appointed to the Gardiner chair of physiological chemistry As a teacher he was “ almost deceptively good ”, as the Principal of the university put it in his tribute last week

“ Neither in the lecture-theatre nor elsewhere was he anything of an orator But his words were so beautifully ordered that only when his students came to work over his material for themselves did they discover how difficult were some of these apparently simple ideas In the laboratory he had swift curiosity, ingenious mind, and contriving hands, happily employed in the experimental work of the school on the borderland of the natural and the biological sciences ”

In 1947 the faculty of medicine was faced with new duties and wider responsibilities, the new health service was to alter the administration of the teaching hospitals, and the opportunities for postgraduate education were to be extended The faculty felt the need for the support and counsel of a full-time dean, and Wishart was their unanimous choice He accordingly resigned his chair to take up his new appointment, to which he added the additional charges of directorship of postgraduate medical education in Glasgow and membership of the General Medical Council Of his bearing and achievements in this new career J W H writes

“ George Wishart set himself a programme of work which would have been beyond most men's will and energy As Dean of the faculty, his leadership was truly that which aspired above all to serve *His colleagues know how well he served* Faculty meetings kept to the point and did not drag on until exhaustion produced resigned assent or snap decisions On the contrary, the Dean saw to it that he was well prepared beforehand He not only knew the business; he knew also what was likely to be said for and against any proposition, and he knew pretty well who would be saying what If he foresaw trouble, he would arrange for quiet consultations beforehand Thus, business came to the faculty well considered The issues were not cut and dried, but there were few surprises for the Dean. Even the most difficult matters were usually settled quickly and amicably, and if it emerged that this would not happen he was ever ready and keen to take the matter away for further study—which meant that he put in even more hard work and consulted still more of those whose interest was involved The meetings went quickly and smoothly not because he avoided discussion, but because he provided the work which kept the discussion informed and made the opportunities for all whose concern was serious to give their minds to the problem in advance Each year, the faculty required less than ten seconds to re-elect him dean after he and the clerk had withdrawn, this was only one of the measures of the confidence and gratitude of his colleagues

“ He was ever careful of the best interests of the students —the mediocre and the disappointing as well as the industrious and brilliant Many of the students from overseas owed him a particular debt, and he was much gratified when one Nigerian named his villa after him and sent him a photograph showing the name clearly marked in big letters on the gateposts It was a well-conceived gesture, for Wishart was always keen to see people get what they desired if he thought that they had a good or even a fairly good claim Unduly high rates of failure in the examinations always disturbed him, and the last explanation of these that he would ever accept was that the students were a poor lot Even if all his colleagues did not accept some of his alternative propositions, they admired and respected his faith in the students and his advocacy of their case

“ He directed postgraduate education in Glasgow with great care and thought He never allowed schemes to become grandiose or to flourish merely because they looked wonderful on paper He was ever aware of the need to keep education medical and realistic as well as to have it scientific and polished He admired high standards but he was critical of claims that overreached realities Teachers who had something real to offer could always count on his welcome and his protection, especially if their position might have made them liable to be overlooked

“ On the Regional Hospital Board he gave hours of devoted service, taking scrupulous care over the anxious matter of all appointments, including the most junior Wishart was anxious to support the right cause and to do it for the right reason His fairmindedness made him an ally worth having in any debate or administrative battle Every now and then he would telephone and say ‘ Listen now—don't explode—just listen and tell me how you think this one would go ’ ‘ This one ’ often proved to be a bureaucratic proposal that would be bound to rouse righteous professional indignation ‘All right,’ Wishart would say, ‘ keep calm, don't worry, I think I know now what to tell them That's all I wanted ’ And so many potential wrangles were happily averted by his quiet watchfulness over professional interests and by the good name he made among administrators for his fairminded advice

“ His colleagues know that they will miss his service and his leadership, they have still to discover how great their loss is ”

This later absorption in administration tended to divert attention from the merit of his earlier research In assessing this work R C G writes

“ A generation or so ago medicine was still very much an empirical art Many medical men viewed askance the disturbing intrusion of chemistry and of physics into the preclinical discipline of physiology with its lusty offspring biochemistry Wishart, on the other hand, was instinctively at home in the physical sciences—in chemistry, in physics, and in mathematics It was very much his pleasure to apply physical techniques to the solution of biological problems His studies with Thunberg in Lund gave him a continuing interest in biological oxidations and reductions and in the conditions governing enzyme action. He also did some work on the metabolic products of muscular activity; he designed a glass electrode for measurements of pH.

"Perhaps the biophysical approach appealed rather more than the biochemical approach. In the '20s the impact of electronics on biology was just developing, everyone built a wireless receiving set. But Wishart turned this new hobby to good account in the laboratory, with an electronic oscillometer he made most valuable measurements of the blood-pressure in different parts of the human body. Quite a different style of gadget, but still showing the flair for the physical approach, was a pursuit meter, useful both in physiology and in psychology, and well in advance of contemporary design.

"However, indirect calorimetry was Wishart's real love. There was no longer any doubt about the validity of the technique, but a whole host of biological problems clamoured for attention. The actual amount of the energy expended by human beings in different tasks under various conditions offered a wellnigh inexhaustible reservoir of topics for research. In the laboratory he helped to design and build a walking platform and a bicycle and other types of ergometer. The mechanical efficiency of the human muscular machine was a somewhat more academic problem, and the validity and usefulness of the conception of a basal metabolic rate was, and still is, both an academic and practical issue.

"All Wishart's scientific work had an elegance born of meticulous care and scrupulous precision. To this was added a fastidious dislike of loose assumptions, uncritical argument, and anything which smacked of self-advertisement. The work he did for his university and for the medical services was at the expense of scientific work of the highest calibre: one can well regret the scientist lost in the administrator."

Professor Wishart died on July 18. He leaves a widow, who was one of his colleagues in his department, and two daughters one of whom is a doctor.

KEITH CHITTY

M.B. Camb., F.R.C.S.

Mr. Chitty, who was appointed consultant surgeon to the Mid-Worcestershire group of hospitals last December, died at his home in Chaddesley Corbett, near Kidderminster, on July 9, at the age of 38.

He was the son of Mr. Hubert Chitty, consulting surgeon to the Bristol Royal Infirmary, who survives him. He was educated at Clifton College, and gained an exhibition at Peterhouse, Cambridge, in 1938. From there he went to University College Hospital, where he won the Erichsen prize in practical surgery. He qualified in 1943, and soon afterwards joined the R.A.M.C. He landed in Normandy on D-1 and was medical officer to the engineers who constructed Mulberry Harbour. He served throughout the campaign and later went to India. After his return in 1947, he spent five years as a registrar at U.C.H., serving successively under Prof. R. S. Pilcher, Mr. Cecil Flemming, and Mr. H. R. I. Wolfe. In 1952 he went to the United Bristol Hospitals, and he held the post of senior registrar to the genitourinary department until 1955, when he became senior surgical registrar at the Bristol Royal Infirmary and the Children's Hospital.

W. M. C. writes:

Keith had served a long and arduous apprenticeship in making himself an accurate and efficient surgeon. He never pushed himself forward, but he was beloved by us all for his forthright and diligent approach to his work, and his unassuming competence made him the best of colleagues. He never blamed anybody else if things went wrong, and no night was too long or operating-list too heavy for his enthusiastic willingness to give everything he had got to serve his patients. His colleagues at Kidderminster quickly accepted him as an efficient and reliable surgeon, and he was welcomed there both professionally and socially.

Mr. Chitty leaves a widow.

Notes and News

ASME

THE first conference of the Association for the Study of Medical Education[1] will be held at the Royal College of Physicians of London, Pall Mall East, S.W.1, on Thursday and Friday, Sept. 25 and 26. The theme chosen for the meeting is Experiment in Medical Education.

Prof. Robert Platt, P.R.C.P., will take the chair at the opening session when Sir Russell Brain will give an inaugural address. Other speakers will include Dr. G. P. Berry (Harvard University), Sir George Pickering, Dr. Nicholas Malleson, Prof. G. M. Bull, Dr. J. N. Morris, Prof. T. Hale Ham (Western Reserve University), and Prof. B. Rexed (Uppsala University).

The conference is open to members of the association and others, and applications should be sent to Dr. John Ellis, the hon. secretary, at the college. Further particulars will be found in our advertisement columns for July 19 (p. 38).

BRUCELLOSIS

THE third report of the F.A.O./W.H.O. Expert Committee on Brucellosis,[2] drawn up at a meeting in Lima, Peru, in October, 1957, witnesses to the continuing great importance of brucella infection of animals and man in many countries of both hemispheres, but it also records important advances in the prevention and control of such infections, particularly in regard to bovine brucellosis (contagious abortion) in the United Kingdom, the U.S.A., Canada, the Netherlands, Scandinavia, and a number of other countries.

In some of these the bovine disease has been eradicated, or almost eradicated, by means of vaccination with an attenuated live vaccine (S19) followed eventually by slaughter. It has been estimated that in the U.S.A. losses from bovine brucellosis have been reduced from $100 million in 1947 to $40 million in 1957. The disease in man has also decreased, though not always at the same rate: in the United Kingdom the lag, so far as can be ascertained, seems to be particularly great.

With regard to the transmission of infection from animals to man two aspects are specially considered in this report—first, infection through fresh goat's-milk cheese, which is the chief infecting agent in some Central and South American countries and elsewhere, and secondly the importance of previously unsuspected animals, especially the hare, as agents of spread.

The committee lay down useful criteria for judging the efficacy of any therapy for undulant fever—criteria which are particularly important in a disease which before the introduction of antibiotics often terminated suddenly and spontaneously, and which under treatment by antibiotics often seems to behave similarly but yet relapses. The report sounds the salutary warning: "All forms of antibiotic therapy and chemotherapy currently in use are merely suppressive of the infection. ... The indiscriminate and uncritical administration of antibiotics for brucellosis offers certain hazards." Certain forms of chemotherapy (streptomycin or dihydrostreptomycin with sulphonamides, or the tetracyclines alone) are recommended. The use of corticosteroids for tiding over the toxic phase is mentioned, but extreme caution is urged in the use of these compounds.

In Russia an attenuated live vaccine (S19) has been used for the immunisation of human beings, but the committee regards such a procedure as still experimental. Of desensitisation with various antigens the committee remarks that "adequate desensitisation is difficult to accomplish and is usually transitory." But in many long-continuing cases chemotherapy is either ineffective or cannot be tolerated by the patient who has developed a high sensitivity to brucella toxins, and in such cases desensitisation is the only therapy available, and in the hands of some workers this has effectively banished the symptoms until the body's defences have restored a "comfortable symbiosis" On the animal side experiments on a large scale with the three vaccines already evolved for protection against caprine brucellosis are urgently recommended

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[1] See *Lancet*, June 14, 1958, p. 1261.

[2] Joint F.A.O./W.H.O. Expert Committee on Brucellosis: third report. *Tech. Rep. Wld Hlth Org.* 1958, no. 148. Pp. 51. 3s. 6d. Obtainable from H.M. Stationery Office, P.O. box 569, London, S.E.1.

Finally in dealing with the interpretation and standardisation of diagnostic tests, the committee emphasises the importance of stating the results of seroagglutination tests in international units per millilitre, in order to facilitate comparison of data given by different methods

HELP FOR MOTHERS

FOR the past ten years a few pioneers have offered training and encouragement, instead of punishment and censure, to mothers who are not making a success of running their homes One of their early ventures, Spofforth Hall[1] near Harrogate, which was run by the Elizabeth Fry Memorial Trust of the Society of Friends, had to close about a year ago when its lease ran out, but the Trust is now opening its successor, which will be known as the Elizabeth Fry Home, at West Bank, Acomb, York The new premises have some advantages over the old Spofforth Hall was a lovely house, West Bank is in York and has smaller rooms and will seem less strange to the families who come for training The Trust will continue to take mothers accompanied by their younger children It hopes to accept those who may have been before the courts on a charge of child neglect as well as those sent by local health authorities who fear the breakup of a family As the home is within the city, the officers of the welfare and health departments will be able to take a greater part in the work than was possible at Spofforth Hall

University of Oxford

On July 12 the degree of B M was conferred on the following

Neville Rosen, M W Price, E H Stubbe, J R Harper, W P Metcalfe, David Negus, Alan Percival, J G Wood, D W C Dove, J C Anderson, James Freeman, P D Oldreive, R P Golding, W G Everett, J C Probert, M J Brown Janet A Bone, Julia D Dawkins, Isabel C A Greig, *M W Moncrieff, *John Dupré, *N H M McKinney, *M E Woolrych, *S D Weisbaum, *Mignon S Marston

* *In absentia*

University of St Andrews

The university court, acting with the Eastern Regional Hospital Board, has appointed Dr D M Green, senior lecturer in bacteriology at Queen's College, Dundee With the post is associated an honorary appointment from the regional board as assistant bacteriologist with the status of consultant Dr Green will take up his duties on Aug 1

Royal College of Obstetricians and Gynæcologists

On July 26 a meeting of the council was held with Prof A M Claye, the president, in the chair The following officers were re-elected

President, A M Claye, hon treasurer, A C H Bell, hon secretary, Ian Jackson, hon librarian, A J McNair, hon curator of the museum, Alan Brews, hon treasurer, Australian regional council, J N Chesterman, hon treasurer, Canadian regional council, G A Simpson, hon treasurer, New Zealand regional council, A M Rutherford, hon treasurer, South African regional council, F N Charnock

The following officers were elected

Vice-presidents, G F Gibberd, S W Maslen-Jones

The following were elected to the membership

Prabhavathy Aiman, Prasannatissa Harischandra Amarasinghe D T C Barber, C T H Barrett, W P Bonnici, John Breeze, J M Brudenell, D Pui-Chee Chan, H J H Claassens, C J T Craig, Dilip Ranjan Das, R M Davie, R F Drake, G R Duncan, G H Ellidge, W H Fernando L H Fienberg, J MacD G Harley, Denys Heginbotham, J B Hemsley, Alice Hsiang-Lien Hsu, P J Huntingford, Sylvia R Ingold, Katherine I Jack, R D Johnstone, E W P Jones, A J Keane, A C Keast, D M D King, Sybil V Kinley, Daphne R Lowe, John McGlone, Sheila Malhotra, Gouri Sankar Mandal, D T Mathews, Charu Chandra Mitra, Diana Montgomery, W P L Morrison, A D Muirhead, Salvino Muscat, Sapugahawattege Henry Piyadasa Nanayakkara, Isabella R Napier, Hannah J Pash, J H Peters, D W Pfanner, Carmen M Rant, D M Reader, W J C Rebello, John St George, Ajit Kumar Sarkar, P C Sutchbury, Jean O Struthers, W M E Tweed Radha Narayan Udipi, Thiagarajah Visvanathan, A W G Weir, Dorothy J Whitney, W G Wicks, Balasubramaniam Yoganathan

British Medical Association

Dr Walter Hedgcock has been appointed deputy secretary of the Association, and Dr D L Gullick and Dr J D J Havard assistant secretaries

Royal College of Physicians of Edinburgh

At a meeting of the college held on July 22, with Dr A Rae Gilchrist, the president, in the chair, the following were elected to the membership

T E Anderson, T N Macgregor, Wilfred Sircus, Pow Meng Yap, M F H Kelleher, Krishna Kumar Gupta, Amin Salim Jureidini, Rathni Vasant Kumar Alwa, Mohammed Abdul Ghani, Mahmoud Mohamed Hassan, J M Hughes, K J Cullen, E A Kauffmann, Jyotirup Chatterjee, Loku Banda Tennekoon Jayasundera, J G Wijeyesekera, Rajeshwar Prasad Sharma, Nirmala Haridas Gopaldas, J D E Knox, Arumakuttige Parakrama Jayasena Weerasekera, Raj Kishore Panda, Jacob Schneider, B W Petty, Akiwusi Abiola Akiwumi, Evelyn Hanam, D A Seaton, R D Catterall, J H A Dwek, Ram Nath Gupta, David Zentkowsky, Hau Cheong Kwaan, Maung Hla Myint, Thanuvelil Scaria Koshy, Anl Ali Hameedi, Dharamvir Narula, Rusi Jehangir Buhariwalla, Chun Thuan Lee, Werner Heinrich Schutt, Harry Stark, Batukrai Gulabrai Gandhi, Yong Kiat Lee, Kranti Prasad Jain

International Association of Gerontology

The first meeting of the European clinical section of this association is to be held at Sunderland General Hospital, from Oct 1 to 4 Further information can be had from Dr E Woodford-Williams, at the hospital, Chester Road, Sunderland

Institute of Laryngology and Otology, London

On Friday, Aug 8, at 5 30 P M at the institute, 330, Gray's Inn Road, W C 1, Dr Ben H Senturia, of St Louis, will speak on diseases of the external ear

Effects of Pollution on Living Matter

The Institute of Biology is holding a symposium on this subject on Sept 25 and 26, at the Royal Geographical Society, Kensington Gore, London, S W 7 Further particulars may be had from the secretary of the institute, 41, Queen's Gate, S W 7

Conference on General Practice

The *Medical World* is holding a conference on general practice in the Victoria Halls, Bloomsbury Square, London, W C 1, on Sunday, Oct 26 Tickets (*10s 6d*) may be had from the conference organiser, 56, Russell Square, W C 1

The Medical Insurance Agency

The 30th annual meeting was held at B M A House, London, on July 24 The report of the committee of management disclosed new records of business done in all branches new high levels of assurances have been negotiated and higher profits have been allocated to medical charities The report ended with a claim that the agency's work is of great service to the profession, that more and more doctors recognise that this is so, and that in reputation and esteem it has never before stood so high

Sir Russell Brain and Sir Cecil Wakeley were elected to the committee Retiring members re-elected were Dr James Fenton, Sir Archibald Gray, Mr A M A Moore, Mr Ronald Raven, Dr Oliver Scott, Mr Ben Thomas, and Sir Henry Tidy Dr Fenton was re-elected chairman, and Dr Henry Robinson hon secretary The report contained an emphatic tribute to the work of the general manager, Mr A N Dixon, and his staff

St Clement's Hospital, Bow

King Edward's Hospital Fund for London are to make a grant of £50,000 to help the North East Metropolitan Regional Board in their plans for developing this hospital as a modern psychiatric hospital

The hospital already has an observation ward and a small unit for cases of psychoneurosis, and as the board think that in the future the hospital will no longer be needed for the general hospital needs of the area, they have decided to extend the psychiatric work with the ultimate object of establishing a modern neuropsychiatric centre for East London, which will provide full facilities for the investigation and treatment of all types of acute mental illness, as well as for teaching and research As a first step it is proposed to refurbish a three-storey block at the hospital which is at present derelict, and to set up a day hospital for old people in the early stages of mental deterioration This unit would be combined with a domiciliary service in cooperation with the local authority Apart from the day hospital, it is intended to provide an inpatient unit for severely disturbed young patients and to extend the occupational therapy and outpatient departments The first stage of the plan will cost about £59,000, and the gift from the King's Fund will enable the board to approach the Minister of Health for approval to embark on this project

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[1] See *Lancet*, 1953, ii, 460

The Lancet · Saturday 9 August 1958

CEREBRAL VASCULAR DISEASE IN THE LIGHT OF MODERN TECHNIQUES *

J St C Elkington
M.D Cantab., F.R.C P

PHYSICIAN-IN-CHARGE, NEUROLOGICAL DEPARTMENT, ST THOMAS'S HOSPITAL, LONDON, S.E.1, PHYSICIAN, THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON, W C.1

Cerebral vascular disease is of great and, one fears, of still growing importance in Western society It would be a fascinating historical study to examine the part it has played in the history of the last two thousand years with its stories of the gradual decline or perversion of powerful regimes and of the violent oscillations of events brought about by the sudden removal of some outstanding personality from the scene of human affairs

Some idea of its importance in contemporary society can be obtained from a brief reference to the Registrar-General's Statistical Review for England and Wales in which the annual deaths from cerebral vascular disease over the ten-year period 1946-55 are compared with those from arteriosclerotic heart-disease and from carcinoma of the bronchus and lung—two disorders much in the public eye at the present time. Fig 1 shows that the toll of cerebral vascular disease in every case surpassed that of the other two, and during the first half of the period exceeded their sum often by a considerable margin American figures tell the same story Wright and Luckey (1955) record that in 1952 there were 172,000 deaths from cerebral vascular disease—a figure exceeding by three times the combined deaths from diabetes and tuberculosis These figures give no idea of the amount of chronic illness and of premature incapacity which, because of its nature, cerebral vascular disease inflicts upon society

Old enemies, like old friends, are apt to be taken for granted and cerebral vascular disease is no exception This is aptly illustrated by an extract from a clinical lecture published fifty years ago (Rose Bradford 1908) Speaking of cerebral aneurysms the lecturer said that these might give rise to no symptoms till they ruptured, adding "These cases are of no clinical interest, they are merely cases of cerebral hæmorrhage" This statement cannot have seemed as unusual in those days as it does today, for twenty years later the speaker was president of this college.

It might be said that the last twenty years have not added greatly to our fundamental knowledge of cerebral vascular disease, but the developments in cerebral and vascular surgery and of surgical techniques, especially radiology, have thrown notable light on its details and have opened up new possibilities both in diagnosis and treatment It is against this changing background that I propose to review the subject, selecting for particular discussion those aspects in which modern techniques have brought greater accuracy in diagnosis and are gradually bringing about a modification of orthodox attitudes towards management and treatment

Classification

To have any hope of success an attempt to review so large a field requires a schema by which the subject may be broken down into manageable subsections, and, while being fully aware of its scientific imperfections, I propose to employ the following classification It will be understood that in any individual patient more than one variant of cerebral vascular disease may exist at the same time

Diffuse
(*a*) Generalised ischæmic brain degeneration from atherosclerosis.
(*b*) Cerebral disorder in arterial hypertension.

Local
(*a*) Focal softenings from ischæmia, including occlusion of minor vessels by thrombosis or embolism.
(*b*) Massive softenings from ischæmia, including occlusion of major vessels by thrombosis or embolism
  (1) Internal carotid artery occlusion
  (2) Basilar artery occlusion.
(*c*) Intracranial hæmorrhage
  (1) Meningeal hæmorrhage
    (i) Extradural
    (ii) Subdural.
    (iii) Subarachnoid.
  (2) Intracerebral hæmorrhage.

Generalised Ischæmic Brain Disease from Atherosclerosis

Though diffuse ischæmic brain disease is quantitatively the most important manifestation of cerebral vascular disease it need occupy only a few moments of our time, for its features are well known and have hardly been affected by modern advances It is essentially the end-result of atherosclerosis with or without hypertension and such occasional aggravating factors as alcohol or head injury.

In many cases it is a disorder of gradual progression but its course may be punctuated by outspoken vascular accidents of greater or less severity

Its most striking feature is progressive mental deterioration. At first the gradual falling off of the individual's innate creative capacity and of his desire and ability to meet new situations, together with a closing in of the mental horizon and an increasing egoism, may seem to be no more than the natural effects of advancing years Forgetfulness, first for recent and then for more remote events, loss of capacity for all but familiar intellectual activities, accentuation of the underlying qualities of the personality, mood changes, decrease in emotional stability, and periods of confusion mark its advance into the realm of the pathological Finally, a state of profound dementia supervenes, differing only in detail from that seen in other conditions of generalised brain destruction This is a picture well known to us all We see it in the world around us It may fall to the lot of any of us to detect its earliest manifestations in ourselves, though it must be admitted that loss of insight is amongst the earliest features of this insidious disorder

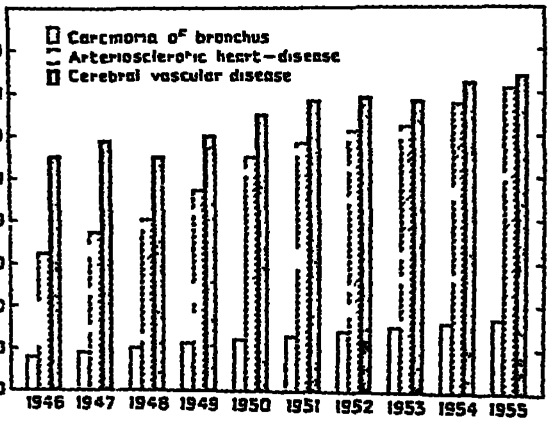

Fig 1—Deaths from carcinoma of bronchus, arteriosclerotic heart-disease, and cerebral vascular disease in England and Wales, 1946-55.

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* The first Lumleian lecture for 1958, delivered before the Royal College of Physicians of London on April 15

Less familiar to many are the physical symptoms which may accompany and sometimes precede the mental change of diffuse ischæmic brain disease Loss of physical agility may pass imperceptibly into lack of balance The natural resilience of the gait is replaced by shuffling steps The voice takes on a monotonous quality which is the prelude to a spastic dysarthria Dyspraxia of the limbs and trunk adds its frustration to the effects of mental confusion and evokes outbursts of weeping or of laughter Years of bedridden dependence upon others for the most elementary necessities of life may precede the patient's final release

Such is a picture that has not changed through the centuries and which seems unlikely to change until we have some effective method of arresting arterial degeneration in general and atheroma in particular

Cerebral Disorder in Arterial Hypertension

This interesting manifestation of cerebral vascular disease, often referred to as hypertensive encephalopathy, may be superimposed upon the background of ischæmic brain disease or may exist independently It may occur in association with severe degrees of hypertension from whatever cause—e g , in essential hypertension, unilateral renal disease, toxæmia of pregnancy, or rare disorders such as porphyria

Its symptoms are both mental and physical, but these share in common a remarkable tendency to fluctuate in severity such as is seldom observed in other forms of vascular brain disease

In the mental sphere, anxiety, confusion merging into delirium, and alterations of consciousness are more conspicuous than dementia On the physical side, epileptic fits either generalised or focal are common Manifestations of local brain dysfunction, such as blindness, loss of speech, and hemiplegia or monoplegia, having all the features of similar events due to vascular accidents, may suddenly make their appearance only to disappear in the course of a few days Hypertensive retinopathy is commonly present, and varying degrees of hypertensive heart-failure may complicate the picture

In spite of much that has been written, the underlying pathology of hypertensive encephalopathy remains obscure If not directly dependent upon the degree of arterial hypertension, it is clearly closely related to this and as with retinopathy it is seldom seen with a diastolic pressure of less than 130 mm Hg The features of the mental picture suggest that we are here dealing with a diffuse process, while the focal symptoms indicate local involvement of portions of the brain The rapid fluctuations in the severity of the symptoms both mental and physical can only be satisfactorily explained by a process which, at any rate initially, is reversible

Œdema of the brain substance and nerve-cell anoxia from arteriolar spasm or from general slowing of the cerebral circulation suggest themselves as possible explanations In hypertensive subjects the cerebral blood-flow is known to be significantly reduced Denny-Brown (1951) believes that the changes are associated with multiple small cerebral lesions associated with small arterial occlusions Pickering (1948) suggests that in cases of acute hypertension œdema of the brain is responsible, whereas in the hypertensive crises occurring in more chronic cases occlusion of small arteries is the cause Foley (1956) finds the histological accompaniments of hypertensive encephalopathy to consist largely of swelling, miliary infarcts, petechial hæmorrhages, and evidence of increased vascular permeability, superimposed upon more chronic vascular lesions

Whatever may ultimately prove to be the correct explanation of the phenomena of hypertensive encephalopathy, its general relationship to the level of th blood-pressure, and in particular to that of the diastol blood-pressure, clearly demands that it should be give consideration in relation to the treatment of hypertensio as a whole

Much has been written in the past twenty years on th treatment of arterial hypertension The era of thoracolumbar sympathectomy was followed by that of ganglion-blocking agents and of other drugs ' Numerous series o cases have been published showing the effect of these procedures on the blood-pressure and on the patient's symptoms No final conclusions can yet be drawn, and no doubt other hypotensive agents await discovery In the series of cases published up to now relatively little reference is made to the effects of hypotensive therapy on the symptoms of hypertensive encephalopathy These, admittedly, are more difficult to measure than the blood-pressure or the manifestations of cardiac embarrassment But on the whole what comment there is seems to be unfavourable Smirk and Alstad (1951) in their comparatively small series state that the incidence of encephalopathic attacks was not obviously altered Shirley Smith (1954) and his colleagues go so far as to include "more than slight cerebral disorder" among the contraindications to the use of hexamethonium compounds Graham and Maxwell (1954), on the other hand, include encephalopathy among their indications for urgent treatment

My own impression has been more favourable to the value of hypotensive therapy in encephalopathy In cases presenting primarily on account of cerebral symptoms it has seemed to me that effective lowering of the blood-pressure, however this is achieved, results in gratifying improvement both in the mental and the physical manifestations of encephalopathy, and I associate myself with those who take the view that even severe encephalopathy is a positive indication for hypotensive treatment, without committing myself to any final opinion as to which method of reducing the blood-pressure is to be preferred

Focal Softenings from Ischæmia

The occurrence of "threatened" or "minor" strokes, often of a repetitive character, is a common event and in the past they have been attributed to the results of occlusion by thrombosis or embolism of the terminal branches of the cerebral vascular tree, to arterial spasm, or, in the presence of hypertension, to small hæmorrhages In many cases this attribution is, no doubt, correct The underlying pathology is diverse, and in conditions such as syphilis or infective endocarditis it may be amenable to direct curative treatment But in the vast majority of such cases the underlying cause is atherosclerosis, and the patient's recovery depends upon the natural powers of readjustment, which are considerable In the past, the degree to which the brain was supplied by end-arteries was overstressed, and Rosegay et al (Rosegay and Welch 1954), among others, have demonstrated very clearly by angiographic studies the extent to which the collateral pial circulation from the anterior and posterior cerebral arteries may supply the area of cortex normally supplied by the middle cerebral artery when this vessel has become occluded

It has long been known to pathologists that in brains examined after such incidents the extent of demonstrable infarction was often much smaller than might have been expected from the clinical symptoms, and that in a considerable proportion of cases of infarction the most careful search has failed to reveal occlusion of the lumen of the artery supplying the damaged area

These observations and the facts which have emerged as a result of the better recognition of the syndromes of occlusion of the carotid and basilar arteries, which will be considered later, have led Denny-Brown and his co-workers (Denny-Brown 1951, Meyer et al 1956, Meyer and Denny-Brown 1957a and b) and later Corday et al (1953, 1956) to postulate the state of "cerebral vascular insufficiency" as an alternative to "vasospasm", which has often been held to explain these occurrences Denny-Brown defines "cerebral vascular insufficiency" in physiological terms as "a state of local or general cerebral blood flow that is unable to maintain the metabolic requirements of the brain during physiological stress" This state may be overt, leading to symptoms and signs during the stresses of normal life, or it may be latent and become manifest only as a result of some special stress—particularly an abrupt fall in the systemic blood-pressure

The condition is the result of narrowing or occlusion, through organic changes, of the arteries—often at a point remote from their terminal distribution This leads to the brain tissue becoming dependent for its blood-supply upon collateral branches from neighbouring vessels, this supply is adequate for ordinary purposes but falls below the critical requirement in the event of a sudden fall in the systemic blood-pressure or a further narrowing of the collateral vessel itself

Denny-Brown and his associates have reproduced the clinical events observed *in man* in a series of beautiful experiments on monkeys after ligation of the common carotid or middle cerebral arteries

Ligation of the middle cerebral artery under normal circumstances produces no demonstrable effects, the collateral circulation through the anterior and posterior cerebral arteries being fully adequate to maintain normal function If, however, in such an animal the systemic blood-pressure was reduced by any means or the oxygen content of the blood diminished by breathing nitrogen a series of events was observed which closely paralleled those of a minor stroke First, changes appeared in the electroencephalographic (E E G) record of the effected area with failure of the normal electrocorticogram and the appearance of an injury potential, both changes, initially, being readily reversible If, however, the hypoxic state was maintained stasis appeared in the smallest venules together with evidence of increased permeability of capillaries Again these changes were initially reversible, but, if the anoxia were maintained, contiguous foci coalesced with the production of an irreversible infarct

Denny-Brown and his colleagues conclude therefore that such infarcts are the result of tissue anoxia and that thrombosis of cortical vessels plays no part in their initial development

USE OF ANTICOAGULANTS

The introduction during the past ten years or so of anticoagulant drugs suitable for prolonged administration has raised the question of whether these drugs have a useful part to play in the subsequent care of patients who have recovered from the effects of a minor stroke Their value seems to be established in the immediate treatment of coronary artery occlusion, and many cardiologists advocate their continued and indefinite use in patients who have recovered from such an incident (e g, Foley and Wright 1950, 1956, Wright 1955, Wright and McDevitt 1954)

However, the conditions in the heart and in the brain are not wholly comparable The liability to an extension or an early recurrence of the occlusion is greater in the heart, whereas the risk of hæmorrhage into a softened area is peculiar to the brain. While recognising its risks and limitations, prolonged anticoagulant treatment is warmly advocated by Wright and his collaborators and by Millikan et al (1955) In the nicely balanced conditions occurring in the brain the point can only be decided on a practical basis

There would seem here to be an admirable opportunity for a properly controlled long-term investigation, which could only be adequately carried out in an institution caring for a large number of chronic sick and senile patients Alternate cases considered to be at risk should be maintained on anticoagulants for the remainder of their lives and the occurrence of thromboembolic incidents estimated annually in both treated and untreated cases throughout their *period of survival*

Occlusion of the Internal Carotid and Basilar Arteries

The brain receives its blood-supply from four arteries—the two internal carotids and the two vertebrals—the latter joining together to form the basilar

The carotids and the basilar are of comparable size and are subject to the same disorders, of which atherosclerosis, aneurysm formation, and embolic occlusion are the chief The three arteries enter into the formation of the circle of Willis, formed by the linking up of their terminal branches by the anterior and the two posterior communicating arteries

In the normal and healthy subject this delicately arranged anastomosis serves to provide an alternative basic blood-supply to all parts of the brain so that either carotid and probably the basilar, provided it is only occluded over a short distance, can be eliminated without disastrous results It has been shown by McDonald and Potter (1951) in the rabbit that the blood-flow through the posterior communicating arteries is normally zero, and that the same is probably true of the anterior communicating The results of angiography suggest that the same is true in man so that in the normal, healthy subject the vascular fields supplied by the two carotids and the basilar remain distinct except at their periphery where they mingle at an arteriolar level

But not all people are normal, nor are they all healthy. Congenital anomalies in the formation of the circle of Willis are common Dandy (1944) stated that a "strictly normal" circle of Willis occurs only in 50% of cases Defects in the posterior communicating arteries are especially frequent Stopford (1916) found this vessel to be absent on one side in 6% and on both sides in 4% of specimens examined Furthermore, the vessels entering into the formation of the circle are peculiarly prone to the premature changes of atheroma Either type of defect, the congenital or the acquired, decreases the efficiency of the natural provision for an alternative blood-supply and increases the risk of disaster should any further occlusion take place Catastrophe may be brought about by some event affecting the efficiency of the circulation as a whole, such as the lowering of the blood-pressure by a blood donation or by an attack of gastrointestinal hæmorrhage (Denny-Brown 1951)

Occlusion of the carotid or basilar arteries may be brought about by a variety of pathological processes, but the results are largely independent of the cause and are determined rather by the anatomical facts peculiar to the individual and by the general state of the cerebral circulation at the time Embolism from any cause may be responsible The carotid because of its length and its position may suffer from the results of trauma Occasionally occlusion occurs in apparently healthy young people in whom the cause may remain undetermined Such incidents are more commonly met with in the carotid than in the basilar artery

Case 1—A healthy young policeman, aged 24, attended hospital on account of weakness and clumsiness of the right hand for two weeks This had become apparent one day on parade when he found himself unable to carry out items of his drill requiring the use of the right hand In retrospect he recalled that for several months he had been liable to drop things out of it On examination at that time the only abnormal sign was loss of fine movement in the right hand with partial loss of postural sense and tactile discrimination in the fingers General examination was negative He made a complete recovery in a few weeks, and the diagnosis of disseminated sclerosis was thought most likely

Some six months later while in Malaya he played a vigorous game of rugby football During the following evening he felt generally unwell After sleeping he woke suddenly in the morning feeling very ill and discovered that he was completely paralysed on the right side and was unable to speak

After several weeks of mental confusion he was flown home where he was found to have a severe right hemiplegia, right hemisensory loss, and a right homonomous hemianopia He had severe mixed dysphasia General examination was still negative A left carotid angiogram showed complete occlusion of the left internal carotid artery 1 cm distal to the bifurcation of the common carotid artery

No cause for this was found Ten years later his general condition remains normal The ætiology of the thrombosis remains unknown

By far the commonest cause of occlusion both of the carotid and of the basilar arteries is atherosclerosis, and the patients are usually in the fifth or later decades of life

Atheroma, though affecting major- and medium-sized arteries generally, has a special preference for certain sites among which the carotid, vertebral, and cerebral arteries are conspicuous As has been so clearly shown by Hutchinson and Yates (1957), in any given case the carotid and vertebral systems are comparably affected and in considering the consequences of occlusion in either territory it is essential to bear in mind what may be taking place in the other In short we have to accustom ourselves to thinking always in terms of caroticobasilar insufficiency The same lesson is brought home by the results of both carotid and basilar angiography in atheromatous subjects

Atherosclerosis affects the carotid and basilar arteries in several ways Firstly, the arteries become tortuous and may eventually be subjected to such sharp kinking that relative stenosis of the lumen is brought about Secondly, the weakening of the media may lead to aneurysm formation Saccular aneurysms of the carotid artery in the cavernous sinus are relatively common, and fusiform aneurysms of the basilar artery are not very rare Such aneurysms may undergo gradual thrombosis which may spread to the lumen of the artery or give rise to embolism in its branches

Finally the intima of the vessel may become ulcerated with the development of a localised mural thrombosis, which in its turn may lead to a massive thrombosis and occasionally to embolism This process of occlusion is often gradual, and cross sections of the artery may show lamination of the clot with recanalisation in its older parts

Although in the respects that have been mentioned the carotid and basilar arteries are similarly affected and must always be considered in relation to one another, the syndromes that result from their final occlusion are sufficiently distinct for them to be considered separately

INSUFFICIENCY AND OCCLUSION OF THE INTERNAL CAROTID ARTERY

The occurrence of massive occlusion of the internal carotid artery has been recognised for many years, but interest in it has been greatly stimulated in the past decade, largely as a result of the development of cerebral angiography It is now recognised to be much common than would have been admitted ten years ago In additi to isolated case-records, small collected series have bee reported by Moniz and de Lacerda (1937), Gurdjian a Webster (1949, 1951), Elvidge and Werner (1951), Johns and Walker (1951), Smyth (1954), Thomson (195 Silversides (1954), and Shapiro and Peyton (1954)

The following brief account is based upon a study the records of 32 cases who have been under the ca either of myself or of my colleagues during the past fi years, as well as of the reported cases Published seri *show general agreement that the condition is common* in males than in females in the proportion of about thre to one, and that the left side is affected more commonl than the right in about the same ratio My own figures a in agreement The majority of the cases occur in the fift sixth, and seventh decades of life, but a significant numbe occur in young adults in their twenties and thirties, henc the average age of carotid occlusion is significantly lowe than that of basilar occlusion *This extension into younge* age-groups is partly accounted for by trauma, but in considerable number the causation has remained in doubt Antoni (1941) and Krayenbuhl and Weber (1944) hav attributed such cases to thromboangiitis obliterans, bu none of their patients has shown evidence of this diseas elsewhere in the body or any of the ætiological feature characteristic of it The majority of workers view the accuracy of this attribution with doubt

There is general agreement that the principal ætiological factor is atherosclerosis, which may manifest itself in the early decades of life, particularly in the neighbourhood of the bifurcation of the common carotid artery

The clinical picture of carotid thrombosis varies within wide limits

At one extreme are the cases which present *themselves in* the form of massive contralateral hemiplegia coming on rapidly without warning and usually associated with depression or loss of consciousness Gowers (1888) remarked on the relative rareness of such cases If consciousness is sufficiently preserved, contralateral sensory disturbance and not infrequently homonomous hemianopia may be demonstrable With a right hemiplegia severe dysphasia is the rule Severe supraorbital headache may occur on the side of the diseased artery Not uncommonly a unilateral or generalised convulsion heralds the onset Blindness in the ipsilateral eye with narrowing of the retinal arteries and subsequent optic atrophy, although pathognomonic of carotid occlusion when it occurs, is relatively rare since the circulation through the ophthalmic artery is usually maintained either from the opposite internal carotid through the anterior communicating artery or by anastomosis with orbital branches of the external carotid Occasionally papillœdema is present

In patients who survive the immediate effects of the stroke, recovery sets in after a week or ten days and continues for *many months* The hemiplegia shows considerable improvement especially in the leg, the arm remaining severely affected and the hand useless

Where the major hemisphere has been damaged, the dysphasia improves but usually persists in some degree indefinitely, especially as regards spoken speech, and with it is found some mental deterioration and euphoria Hemianopia may or may not persist, *and if it does is likely to* involve the lower more severely than the upper quadrants

The picture thus comes to resemble that of occlusion of the middle cerebral artery, for which it is often mistaken Subsequent angiograms of the unaffected carotid artery may demonstrate the filling of the anterior cerebral artery on the affected side through the anterior communicating artery

Case 2 —A previously healthy man of 33, six weeks before admission, was given a tablet of 'Seconesin' on account of anxiety symptoms, to which he was subject This was followed in fifteen minutes by wide-spread urticaria He was given an injection of adrenaline which enabled him to go to sleep Four hours later he had a fit in his sleep and on being woken next morning he was found to be drowsy, totally aphasic and paralysed on the right side of his body When examined he was euphoric and still showed severe dysphasia Vision and the visual fields were full He had a right hemiplegia, complete in the upper limb and severe in the face and lower limb, together with slight general diminution of sensation on the right side of the body General medical examination was negative Blood-pressure 130/80 mm Hg

A left carotid angiogram showed complete occlusion of the internal carotid artery $^1/_2$ in above the bifurcation of the common carotid This was confirmed by operation

Subsequently the patient's condition has improved somewhat

At the other extreme carotid occlusion may cause no neurological symptoms at all Such an occurrence, in a man dying of cancer, was recorded with expressions of surprise by Willis himself, who also noted that the patient had been troubled by severe headache on the opposite side of his head It has long been known that in the majority of people surgical ligation of the internal carotid artery can be carried out with, at most, transient contralateral hemiparesis

Under such circumstances the collateral circulation through the anterior and posterior communicating arteries must be sufficient to maintain normal function. As has already been said, congenital defects or degenerative changes in the circle of Willis may interfere with the efficiency of this compensating mechanism The likelihood of hemiplegia occurring after carotid ligation thus increases with increasing age and is correspondingly lessened when the process of occlusion is gradual

It is not possible to state with certainty what is the incidence of such symptomless thrombosis, but Hultquist (1942) found occlusion of one carotid in 4 4% of 1300 routine necropsies, and Fisher (1954) found complete occlusion in one or both internal carotids in 28 (6 5%) of 432 unselected necropsies

Between these two extremes carotid occlusion more commonly shows itself in one of two recognisable clinical forms which may also occur in the presence of stenosis of the artery and before the lumen has become completely occluded

The first, and by far the commonest, is that of transient episodes of unilateral disturbance recurring at irregular intervals over many months or years For this syndrome Ramsay Hunt (1914) coined the appropriate phrase "cerebral intermittent claudication" Of these episodes the commonest is transitory numbness or weakness of one hand Sometimes this will involve simultaneously the same side of the face or the whole half-body, and at other times the hemiplegia though transient may be complete

The right side of the body is much the more commonly affected since the underlying change more often affects the left carotid, and right-sided attacks are usually associated with temporary loss of speech. Such aphasic attacks may be the sole symptom

Other patients may report transitory loss or partial loss of vision in one eye, which may be mistaken for migraine—a mistake made easier by the common occurrence at the same time of unilateral headache

Others may notice attacks of "dizziness", by which they mean a feeling of confusion and impairment of consciousness rather than of vertigo Rarely, fits—focal or general—may occur.

Case 3 —A previously healthy man of 67 gave a history of four transitory attacks of weakness and numbness on the left side of the body in four weeks The first episode came on without warning and consisted of sudden loss of power in the left hand and arm lasting only a few minutes In subsequent attacks there was also numbness throughout the left half of the body During the same period he noticed a tendency to bump into objects on his left and also rather severe intermittent headaches On examination the only abnormal sign was a partial left homonomous quadrantic field defect A right carotid angiogram showed complete occlusion of the right internal carotid artery

The exact explanation of these transitory episodes was for some time disputed They clearly could not be explained by thrombosis of the carotid artery as such since they might last only for seconds or minutes The theory of "vasospasm" in the distal branches of the diseased artery has been much canvassed, especially by French and other Continental writers, on the analogy of the arterial spasm which has been observed to occur on puncture or other injury to the arterial wall But direct evidence of such vasospasm was lacking, and such measures as stellate block or stripping of the nerve plexus in the adventitia of the artery have not, in the experience of most workers, proved successful in preventing such attacks Some cases may be due to embolism into the distal branches of the affected carotid, but usually the attacks are too frequent, too stereotyped, and too transient to be explained on this basis

The more satisfactory explanation is that of Denny-Brown who, as we have seen, believes them to be due to transitory ischaemia from failure of a collateral circulation which has hitherto maintained an adequate blood-flow in the distal branches of the occluded artery He believes that the collateral circulation fails as a result of some decrease in the general cerebral circulation such as may follow a fall in the systemic blood-pressure or a decrease of the cardiac output from any of a wide variety of causes

This explanation is the more satisfying since we now know that these attacks may occur in cases of carotid stenosis, before actual occlusion of the lumen has taken place, and since they have now been so exactly reproduced experimentally

Finally, occlusion of the carotid artery may give rise to a gradually developing contralateral hemiplegia, initially most severe in the hand and face and often associated with dysphasia In time the whole half-body is affected but the leg remains less damaged than the arm In such cases focal or unilateral fits may occur, and headache on the side of the diseased artery may be severe Such patients are usually thought to have a cerebral tumour, and it is during their routine investigation by angiography that a considerable number of the recorded cases of carotid occlusion have been discovered

Case 4 —A woman of 50 was admitted for investigation because she was thought to have a cerebral tumour Previously healthy, she was noticed some five months before admission to be becoming forgetful and apathetic After some weeks she was reported to have had two seizures in one of which she became generally rigid and in the other she lost consciousness and shaking developed in the right arm and leg Gradually a right hemiplegia developed, and a few days before admission her speech became disturbed and finally lost

On examination she was drowsy and severely dysphasic She had a right homonomous hemianopia without papilloedema, and a right hemiplegia, complete in the upper limb and severe in the lower limb General examination was negative Blood-pressure 110/70 mm Hg

Ventriculography was first performed with negative findings Bilateral carotid angiograms revealed thrombosis of the left internal carotid artery immediately distal to the origin of the posterior communicating artery She survived and showed slight improvement in the severity of her hemiplegia

Clinical Confirmation

In suspected cases of carotid occlusion the diagnosis can sometimes be confirmed by palpating the vessels in the neck (Ramsay Hunt 1914) If the common carotid artery is also involved absence of pulsation at the level of the bifurcation as well as in the superficial temporal and facial branches of the external carotid artery may be readily demonstrable If the internal carotid artery only is involved the difference on the two sides may be detectable, but confusion with the external carotid artery and its major branches makes the test difficult to apply and unreliable in its results

Palpation of the internal carotid artery from the pharynx (Gurdjian and Webster 1949) is a test most observers have found unsatisfactory Decrease in the arterial blood-pressure in the optic fundus may be demonstrated by digital or instrumental pressure on the eye during ophthalmoscopic examination Compression of the opposite carotid artery may be followed by immediate impairment of consciousness and if persisted in by convulsions, but this test should be used with restraint

Absolute Confirmation

Absolute confirmation of the diagnosis can be made by carotid angiography or by surgical exploration It is the development of the former technique that has revealed the relative commonness of carotid occlusion and of carotid stenosis and has stimulated contemporary interest in the subject

The obstruction is usually at the level of the bifurcation of the common carotid or within 3 cm above it (fig 2) In 22 patients Thomson (1954) found this to be the case in 16 cases, 5 occurring in the carotid syphon and 1 in the common carotid artery

In addition to the cases in which complete occlusion of the lumen is demonstrable, stenosis of the artery through the presence of an atheromatous area of the wall and a mural thrombus can sometimes be detected (fig 3)

INSUFFICIENCY AND OCCLUSION OF THE BASILAR ARTERY

The results of occlusion of the basilar artery have much in common with those of occlusion of the carotid artery Here, too, the important ætiological factors are embolism and atherosclerosis, the latter being much the more common The average age at onset is higher than in the case of carotid occlusion Cases of thrombosis below the age of 50 are rare Interest in the subject was greatly stimulated by the paper of Kubik and Adams (1946) based on a clinico-pathological study of 18 cases examined at necropsy But the clinical picture associated with basilar occlusion had long been recognised, as the following quotation will show

> "In occlusion of the whole basilar the limbs of both sides are usually affected Sometimes at the same time, sometimes successively in the course of a few days The limbs on one side, for instance, may become weak and improve, a day or two afterwards the other side becomes weak, and then there is again loss in the side first affected The affection of the facial

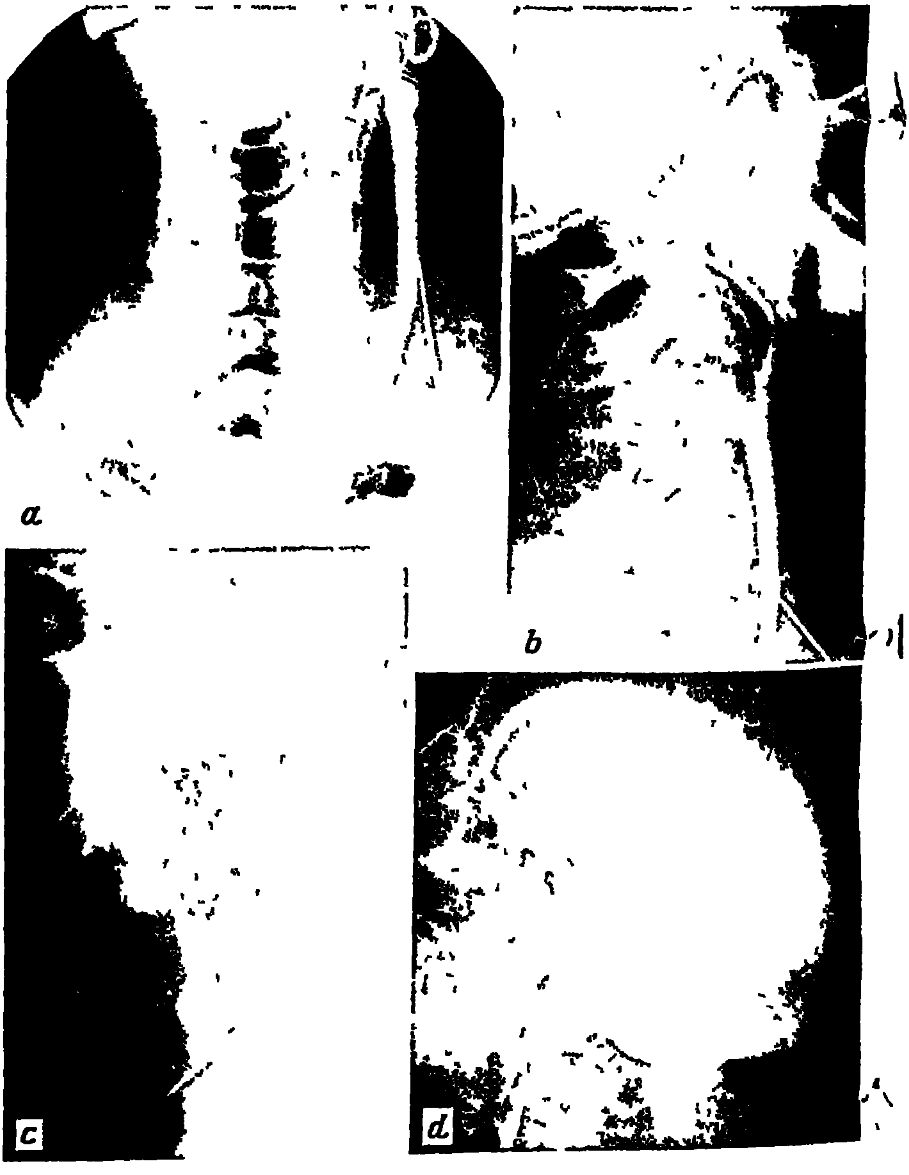

Fig 2—Illustrative examples of occlusion of the internal carotid artery immediately distal to the carotid bifurcation (*a*) in anteroposterior view, (*b*), (*c*) and (*d*) in lateral view

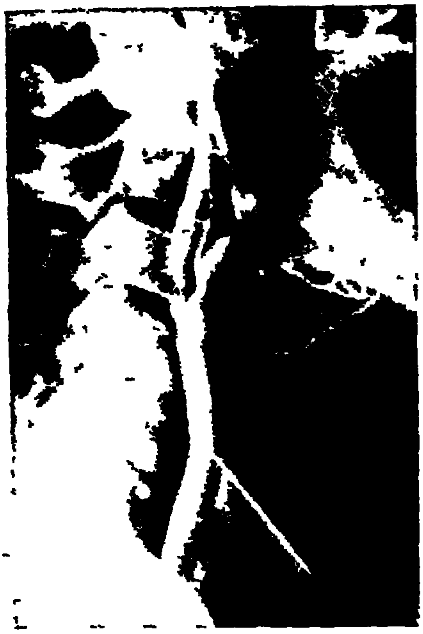

Fig 3—Stenosis of the internal carotid artery from atheroma immediately distal to the carotid bifurcation

or fifth nerve may present the same variations and often does not correspond to the affection of the limbs There is usually considerable impairment of articulation and of swallowing Loss of the conjugate movement of the eyes from palsy of external and internal recti is occasionally observed, with or without palsy of the facial nerve on the side of the affected external rectus When the obstruction involves the upper part of the vessel, as is usually the case in embolism, there are usually ocular symptoms other than conjugate deviation, ptosis, contracted or dilated pupils, with loss of reflex action to light, sometimes transient There is occasionally paralysis of the whole or part of one third nerve or even of both Less common is hemianopia, from extension of the clot along one posterior cerebral beyond the origin of the posterior communicating artery Bilateral loss of sight, theoretically possible, is excessively rare Obstruction of the lower extremity of the basilar is not common, except as an extension of a clot from one of the vertebral arteries The onset of obstruction of the basilar artery is usually attended with a distinct apoplectic seizure, usually transient, it often recurs, and gradually deepens The patient may lie for some days in a state of incomplete coma, can be roused to open his eyes, but does not speak Convulsions occasionally attend the onset, but are on the whole not frequent, they may be general or partial, one limb or one side of the face may escape Rigidity or clonic spasm in the legs or arms is much less common than in hæmorrhage into the pons "

This quotation is taken from Gowers' *Textbook of Nervous Diseases* (American edition) dated 1888, and could hardly be improved upon as a description of the clinical picture of massive basilar occlusion Little needs to be added to it in the light of more recent knowledge, but a few comments may be made The frequent depression or loss of consciousness, even in cases where the occipital lobes are not involved, is of especial interest with regard to the part played by brain-stem structures in the function of consciousness, which was till recently looked upon as dependent upon cortical activity A symptom not mentioned by Gowers and now recognised as occurring in the majority of cases is severe headache, usually fronto-occipital This is probably due to congestion of healthy vessels as a result of overloading of the collateral circulation

Massive occlusion of the basilar artery is commonly fatal, but the period of survival varies over a wide range In many of the reported cases the patient has died within two to three days of the onset of severe symptoms, while others have survived for from six to eight weeks In less severe cases recovery may occur with varying degrees of residual disability, and, as will be seen later, such cases are probably more common than was previously recognised

Case 5 —A man, aged 56, was admitted to hospital on March 1, 1956 Having previously been healthy he sustained, in 1942, a machine-gun wound of the spine which destroyed the spinal cord in its lumbosacral enlargement, rendering him totally and permanently paraplegic.

He made a good adjustment to his disability and led an active life as a school bursar, but developed a chronic urinary infection and was known to be hypertensive with blood-pressure around 230/130 mm Hg In November, 1955, he began to experience recurrent attacks in which for a few minutes he would feel faint and his sight would become blurred Occasionally this blurring was associated with double vision Three days before admission, having had such an episode in the morning, he was found by his wife some hours later unconscious in the lavatory He was cyanosed and twitching on the left side of his body He was admitted to hospital where it was observed that both arms were ataxic and that his speech was disturbed Within a few hours he was unable to speak or to swallow.

When examined in the National Hospital on March 1, he was conscious but unable to speak He could understand and obey simple commands and appeared to have normal fields of vision Apart from the presence of nystagmus, his ocular movements were normal and the fifth-nerve functions were unimpaired There was left facial weakness and the tongue deviated to the left on protrusion As far as examination was possible he seemed to have a spastic weakness of the left arm and some ataxia of both but especially the left Sensation above the waist was normal The lower part of the body had the signs of complete transection of the cord in the upper lumbar region

On the suspicion that the patient was suffering from thrombosis of the right internal carotid artery, a right carotid angiogram was done through the common carotid This was normal except for some irregularity of the vessels suggesting atherosclerosis

In the next two days the picture changed Complete anarthria and aphagia were present The respirations became periodic and the cough ineffective Conjugate deviation of the eyes was lost Both corneal reflexes disappeared and flaccid paralysis developed in the masticatory and facial muscles on both sides Both arms were in a condition indicative of a double hemiplegia

Basilar thrombosis was diagnosed and a vertebral angiogram performed (fig 4) and reported on as follows "A very small quantity of contrast medium is seen at the most superior part of the basilar artery in the lateral view, it is very thin and measures less than 1 mm in diameter In the anteroposterior view the left vertebral artery can be seen to be occluded 4 5 cm from where it forms the basilar This part of the artery has a beaded appearance In the anteroposterior view also the proximal part of the basilar can be seen, and is also narrow and irregular The appearances are very suggestive of a thrombosis of the left vertebral and basilar arteries "

As far as I am aware, this was the first occasion on which occlusion of the basilar artery was demonstrated angiographically during life The patient died six weeks later

At necropsy, in addition to cardiomegaly and the results of a longstanding paraplegia, there was widespread and advanced atherosclerosis The basilar artery was dilated and tortuous and its lumen completely occluded by thrombus below the level of origin of the superior cerebellar arteries, the thrombus extending into the right vertebral artery as far as the mid-medullary level This artery also showed several zones of incomplete obstruction in the neck. In addition there was complete obstruction of the left vertebral artery by thrombus for 2 5 cm prior to its entry into the skull and a 50% reduction of its lumen thereafter The common carotid arteries were atheromatous but not obstructed The right internal carotid artery was atheromatous and about a quarter obstructed immediately distal to its origin. The left internal carotid artery

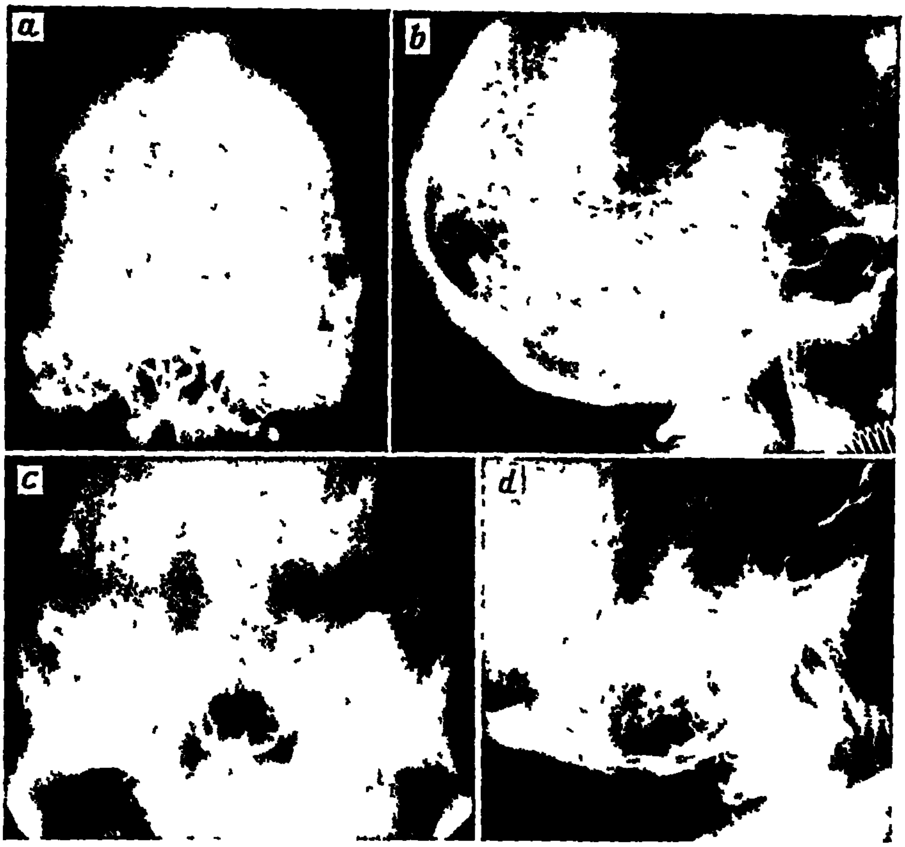

Fig 4—Vertebral angiograms: (a) normal control in anteroposterior view, (b) normal control in lateral view, (c) case 5 in anteroposterior view, showing filling of the left vertebral artery with the basilar artery reduced to a thread and its branches unfilled, (d) case 5, the same in lateral view

was almost completely obstructed just proximal to the carotid syphon The circle of Willis was complete and the posterior communicating arteries were well developed Areas of softening in the brain were of two groups, corresponding to an age of approximately seven weeks and of two days The old lesions were present in the midbrain, pons, and medulla and in both lateral lobes of the cerebellum (fig 5) There was also an area of softening in the right pulvinar, but the occipital lobes and calcarine areas were intact The recent lesions consisted of recent infarction of the cortex supplied by the left middle cerebral artery and also in that supplied by the terminal branches of the left anterior cerebral artery There was a similar area in the cortical zone supplied by the terminal branches of the left posterior cerebral artery

It would appear that this patient had for a long time been virtually dependent upon the right internal carotid and left vertebral arteries for his cerebral blood-supply and had owed his survival to his well-developed circle of Willis and posterior communicating arteries The occlusion of his basilar artery was the culminating disaster in a slowly developing sequence of events Failure of the circulation in the terminal branches of his left middle cerebral, left anterior cerebral, and left posterior cerebral arteries were terminal events in the last few days of his life

The importance of Kubik and Adams' (1946) paper lay, not so much in the fact that it described the clinical picture of fully developed basilar occlusion, though it certainly stimulated interest in it, as that, by careful retrospective correlation of the pathological findings with the history of the cases, it established that many of these patients had, for a considerable time, been having symptoms which, in the light of greater knowledge, could have led to the correct diagnosis being made before the final disaster They thus made it clear that in many cases basilar insufficiency gives rise to transitory symptoms comparable with those in carotid occlusion A similar conclusion was reached by Biemond (1951) from a careful study of 4 cases that came to necropsy

The transitory symptoms in basilar insufficiency are of a nature that might be expected to arise from momentary failure of the circulation in structures normally supplied by its pontine and medullary branches and by the posterior cerebral artery on one or both sides Commonly there are attacks of "dizziness", by which the patient usually means a feeling of faintness associated with a disturbance of balance though true vertigo may occur There may also be tinnitus or momentary loss of speech Numbness on one or both sides of the face may occur or paræsthesiæ referred to one half of the body Brief attacks of monoplegia or hemiplegia may be recorded Transitory diplopia is common Most significant of all are episodes of "dimness of vision" or "blackout" which may signify a transient hemianopia from ischæmia in the field of one posterior cerebral artery or of complete loss of vision if both are involved In association with any of these symptoms headache, sometimes severe, may be experienced Abnormal sensations referred to the abdomen may be noted Frank cerebellar symptoms are rare, presumably because of the rich anastomosis between several vessels in this organ or because of its relative insensitivity to anoxia

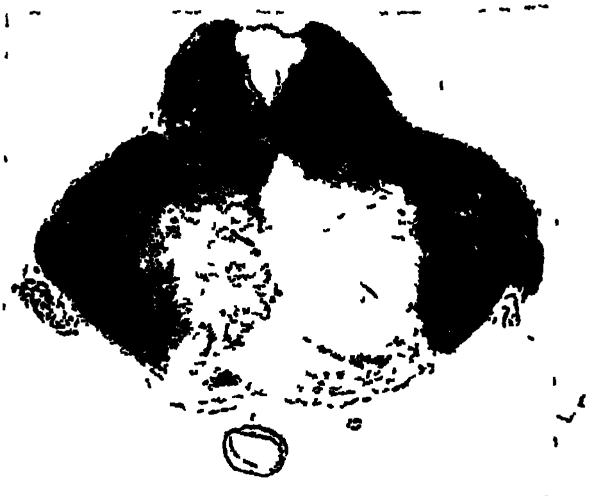

Fig 5—Case 5, showing massive softening in the central area of the pons on the left side

Case 6.—A 49-year-old master plumber, a known hypertensive and a heavy drinker who was found also to be diabetic, was admitted to hospital on account of attacks of numbness of the face over a period of four months. The first attack, occurring in a moment of annoyance, consisted of a feeling of "giddiness" with a sensation of pins-and-needles in both lips on both sides with numbness on the left side of the face, stiffening of the jaw and pulling of the tongue towards the left. He felt suddenly weak and found that he could not talk through stiffness of his tongue. When he tried to walk he staggered but there was no impairment of consciousness. In ten minutes he again felt normal. From their onset these incidents recurred at intervals varying from three days to three weeks with lessening intensity. Questioning elicited the fact that for three weeks he had experienced frequent sensations of sparkling lights passing from left to right in front of his eyes. Throughout the duration of his symptoms he had experienced severe left frontoparietal headaches.

Examination of the nervous system showed no abnormal signs. General examination showed evidence of mild diabetes, obesity, and considerable atherosclerosis. A right carotid angiogram was normal except for some increased tortuosity of arteries. A left vertebral angiogram showed normal filling of that artery, but the basilar artery was narrowed and irregular at its termination (fig. 6). The right vertebral artery was also filled and appeared irregular and narrowed. Anastomotic vessels were seen between the various cerebellar arteries. The film was interpreted as showing the presence of advanced atherosclerosis in both vertebral arteries and the basilar artery with almost complete occlusion of the right vertebral and of the basilar artery at its apex.

This patient continued to improve while in hospital and has remained well since, thus demonstrating that at least incomplete basilar occlusion may be compatible with relatively complete recovery. Numerous other examples in support of this contention might be quoted from recent hospital experience, but in the absence of arteriography or postmortem examination the diagnosis must remain presumptive. A similar view is held by Kubik and Adams (1946) and by Biemond (1951).

TREATMENT OF CAROTID AND BASILAR OCCLUSION

Management and treatment of carotid and basilar occlusion have many points in common and may be discussed briefly together.

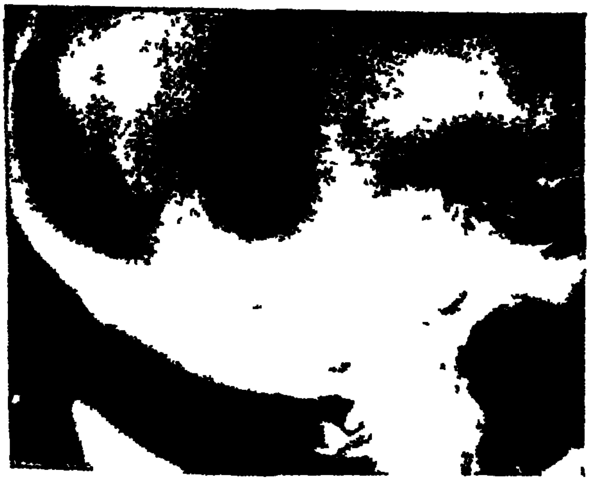

Fig. 6.—Vertebral angiogram in case 6 showing almost complete lack of contrast in the basilar artery and its branches.

In the presence of a major cerebral disaster following such an event, immediate treatment should be directed towards promoting the collateral circulation in the hope of minimising the extent of cerebral infarction. With this in view, nothing should be done to lower the systemic blood-pressure or to impair the vigour of the general circulation.

Attempts to increase the cerebral circulation have been made by the use of a variety of cerebral vasodilator procedures.

Of these, injection of the stellate ganglion or stripping of the adventitia of the carotid artery have been much advocated but are now little used, having been found to be without practical value as well as without sound physiological basis. The use of vasodilator drugs, such as papaverine and histamine, has proved of little worth, and it is notoriously difficult to increase the cerebral blood-flow by such means. The only physiological vasodilating agents are the products of metabolism, of which carbon dioxide is the most active, and the inspiration of 5% carbon dioxide in 95% oxygen for five minutes in every hour is probably the most rational way of promoting the opening up of the collateral circulation to a maximal extent.

The use of anticoagulants here, as in cases of vascular lesions involving the smaller vessels, is a matter of opinion and one requiring carefully controlled observation. When the diagnosis of carotid or basilar occlusion is established, and provided that the patient is not dangerously hypertensive, there seems to be a strong theoretical case for anticoagulant therapy. This is particularly true of cases in which transitory episodes are occurring but in which serious infarction has not yet taken place, as well as of cases due to embolism. In America the use of anticoagulants in such circumstances is certainly increasing.

In the longer-term management of cases of carotid occlusion we have nowadays to consider the possibilities of direct surgical intervention in the form of resection of a portion of the artery or of the removal of the clot followed by an attempt to re-establish the blood-flow with or without an arterial graft. Cases of this kind were reported by Strully et al. (1953), Eastcott, Pickering, and Rob (1954), and Edwards and Rob (1956).

Rob and Wheeler (1957) have recorded their experience of this procedure in 27 cases of carotid occlusion. Clearly with modern technical methods, including artificially induced hypothermia, the surgical procedure is not unduly hazardous. Satisfactory results can only be obtained before the thrombosis has extended into the intracranial portion of the artery, and as one might expect the best results are obtainable in those cases where the diagnosis has been made before irreversible changes have occurred in the brain, and particularly in cases of carotid stenosis.

This method of treatment cannot yet be applied to cases with comparable conditions in the basilar artery, but in view of the advances of the past twenty years it does not seem fantastic to hope that in due course methods may be found to overcome what at present seems an unsurmountable problem.

(The references will appear at the end of the second lecture.)

EXTRACORPOREAL CIRCULATION IN INTRACARDIAC SURGERY:

A COMPARISON BETWEEN TWO HEART-LUNG MACHINES

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IN many centres in the U.S.A. open heart surgery with the aid of heart-lung machines is undertaken almost daily. The very frequency and repetition of such operations has considerably reduced their risks, and in the less complicated cases their mortality-rate is now similar to that of other major surgical procedures.

In the pioneer stage fatalities could most often be attributed to the mechanical device. Subtle changes in the blood-clotting enzymes were common: pyrogenic surfaces, direct trauma to blood in turbulent pumps, inadequate flow or oxygenating capacity, and perhaps minute oxygen embolism all contributed to the early difficulties. But pump-oxygenators have improved, and several different models have been developed which cause less trauma to the blood and largely avoid the other difficulties. With the improved machines, the proficiency of the team has become relatively more important: their teamwork and experience begin to matter more than the choice of apparatus. Where open-heart surgery with a heart-lung machine has become a normal surgical procedure, morbidity and mortality depend chiefly on case-selection and surgical management.

At Stanford University Hospital during 1955–56 tests of several heart-lung machines established a preference for oxygenating the blood by surface filming rather than by introducing oxygen bubbles. Out of this study came the design of a machine using disposable plastic surfaces for oxygenation, in a modification of the principle advanced by Gibbon (1954). The Osborn machine (Osborn et al. 1957) was intended to have all the advantages of the Gibbon machine without its most serious disadvantage—i.e., the fact that surfaces which may be difficult to clean properly are repeatedly in contact with blood. The Osborn machine, together with a rotating-disc machine designed by Melrose (1955) at the Postgraduate Medical School of London, have been in routine clinical use since May of last year—the former throughout this period but the latter only since December. They have been operated by the same team and are at present used alternately. No particular selection of cases has been attempted save that when patients are large the Melrose machine is preferred because of its greater oxygenating capacity.

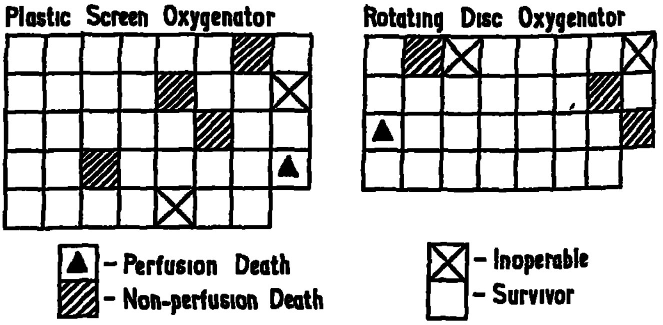
From a study of the 100 cases operated on during this time, no substantial difference in mortality or morbidity or any other measurable variable could be detected. As technique developed with experience, each machine could be expected to provide an entirely satisfactory operative environment, and the choice between them could thus be made only on grounds of convenience, cost per perfusion, and other administrative considerations.

On such grounds it has been decided to adopt the Melrose machine with an important change in its construction, so that all substantial parts in contact with blood may be made disposable and that they may be sterilised by autoclave. The oxygenator is to be of metal covered with 'Teflon', and disposable discs of stainless steel replace those now made of plastic. These requirements are judged essential for the proper maintenance and safety of an apparatus used more than five times a week. With this alteration, it is hoped that from now onwards this machine can be used for all intracardiac operations at Stanford University Hospital which require extracorporeal circulation of the blood.

Results of Operations

During the comparison of the two machines, 70 patients, in age between 4 months and 52 years and varying in size between 0·26 and 2·0 sq. metres, were operated on (table I). While the majority were in good health, there was no rigid exclusion of those not so fortunate: 3 were in heart-failure, 6 were undergoing a second or third thoracotomy, and pulmonary disease was present in several, as was marked cyanosis, which was extreme in 2. Though the acceptance of bad-risk patients is necessary, proper perspective is obtained only if, in the initial experience, they are interspersed with those offering a good chance of cure.

In presenting the results (see figure), we have followed a format used by Kirklin et al. (1958), and like them have attempted to attribute to each death its true cause. Where no satisfactory clinical or pathological justification for the death was found, it was attributed to the perfusion. Some deaths have occurred in patients found to have lesions which defied correction. In the remainder, a review of the clinical course and necropsy findings showed sufficient cause to exonerate the perfusion. The figure shows this analysis. The mortality in this series is better than 19%, and when inoperable cases are excluded it is better than 13%.



The inoperable problems were a tumour of the left ventricle, the removal of which left too little muscular tissue to support life, 2 single ventricles which could not be anatomically divided and total anomalous pulmonary venous return in an infant. One of the 2 deaths attributed to perfusion was in a patient with an interventricular septal defect and moderate pulmonary hypertension. The other was in a patient with the tetralogy of Fallot who was markedly cyanotic. In neither could a satisfactory reason be given for their demise, one eighteen hours after operation and the other on the third postoperative day.

Among the causes found for failure in the remainder have been cardiac tamponade due to inadequate venting of the pericardium and retrosternal space, ineffective blood replacement during the postoperative period, and, in 1 case, massive infarc-

TABLE I—DISTRIBUTION BY ANATOMICAL DIAGNOSIS

—	No. of cases	No. surviving
Interventricular septal defect	20	17
Tetralogy of Fallot	14	11
Single ventricle	2	0
Interatrial septal defect (with associated conditions)	18	18
Left-ventricular/right-atrial shunt	5	5
Common atrioventricular canal	1	1
Total anomalous pulmonary venous return	1	0
Pulmonary stenosis	4	4
Pulmonary stenosis with atrial septal defect (cyanotic)	2	0
Mitral insufficiency	1	0
Left atrial tumour	1	1
Left ventricular tumour	1	0
Total	70	57

TABLE II—AVERAGE PLATELET-COUNT IN THOUSANDS

—	Plastic screens	Rotating discs
Before bypass	234	217
After bypass	144	130
One hour after bypass	175	165

tion of the right ventricle due to interference with its blood-supply. Heart-block has undoubtedly contributed in 2 instances but has not in itself been the reason for death. The presence of an unsuspected patent ductus arteriosus, in a patient operated on for interventricular septal defect, contributed to another failure. In this instance, equal pressures obtained both in the aorta and in the pulmonary artery which was enormously dilated.

Pulmonary complications have been little in evidence, and, save in the patient whose left ventricle, after the removal of a tumour, was deficient in muscular tissue, we have not been plagued by pulmonary œdema or abnormal bronchial secretions. Respiratory embarrassment occasioned by the thoracotomy has been greatly reduced by using the median stenotomy incision (Gerbode et al. 1958), and little difficulty attends convalescence on this score. We have noted, however, temporary respiratory acidosis when nursing care has not sufficiently encouraged breathing.

Post-perfusion Syndrome

We have not encountered "the syndrome of sudden death": no patient whose immediate postoperative condition was satisfactory deteriorated unexpectedly. More familiar has been a "post-perfusion syndrome", characterised by a persistent hypotension of mild degree, by restlessness and hyperpyrexia, and by mild cyanosis associated more obviously with the poverty of the peripheral circulation rather than with any respiratory cause. Review of the course of operation in the 5 patients with this syndrome has underlined the hypotensive element. Each was hypotensive during anæsthesia and surgery, even before perfusion was started. Neither blood-transfusion nor vasoconstrictor drugs had more than a temporary effect at this time.

During the period of perfusion, in spite of a perfusion-rate known to be adequate (2·3 litres per sq. m. per minute) the systolic blood-pressure remained below 70 mm. Hg and could not be raised by increasing the flow-rate. After perfusion the hypotensive state persisted. Errors in restoration of blood-volume were unlikely because the patients were accurately weighed after operation. 2 patients with this syndrome failed to survive and are classified as perfusion deaths, 2 others whose death is put down to surgical causes showed essentially similar signs; in another, these signs were of milder degree and progressively diminished, leading to full recovery. All were patients in whom considerable surgical correction was required, all had extensive refashioning of the pulmonary-outflow tract and each had a considerable return of blood from the open heart through bronchial-artery anastomoses. This latter problem is regarded as important, for blood collected from the open heart must undergo additional trauma, and embolism with air rather than with oxygen will be possible on its return to the extracorporeal circuit. That it should be returned is perhaps debatable, but certainly this is essential in all cases where such collaterals are prominent. It has been our policy to let such blood settle in a reservoir for as long as possible before returning it to the perfusion.

Elective Cardiac Arrest

Elective cardiac arrest with potassium citrate (Melrose et al. 1955) has been used routinely for defects involving the interventricular septum and whenever blood-loss has been excessive or has prevented a good view of the operative field. In this series, it has been used on 36 occasions. 2 patients have undergone repair of an interventricular septal defect twice, and on each occasion cardiac arrest was used. With necessary precautions (Gerbode and Melrose 1958) it is established that it is helpful, reliable, and safe.

The Hæmatology of Perfusion

Postoperative hæmorrhage has not been a problem, the average loss of blood being 890 ml. with extremes of 80 ml. and 4050 ml. 3 patients were reopened for such bleeding, and in 1 an obvious focus was found in the cardiotomy wound. The 2 others had undergone open heart surgery within the previous six weeks and both oozed considerably at the successful second operation. In each case evacuation of blood clots was followed by little further bleeding and full recovery.

Coagulation abnormalities have been slight and have required no unusual management. In routine investigations the following observations were made by one of us (H. A. P.).

In an attempt to compare the effect of the two types of pump oxygenators on the circulating blood, changes were followed in the levels of plasma-hæmoglobin, blood platelets, fibrinogen, and other plasma-coagulation factors. During the early part of this study, all the donor blood was approximately four hours old. More recent bypasses used blood collected twenty-four hours in advance. There was no difference in the hæmatological changes induced that could be ascribed to the age of the donor blood.

Fibrinogen loss, which was an important source of clotting difficulties with early experimental pump oxygenators (Osborn et al. 1956), did not occur with either the Osborn or the Melrose machine.

Platelet loss during the bypass occurred to the same degree with both (table II)—never to levels low enough to be responsible for hæmorrhage. After operation, the counts returned rapidly towards the control values in all but 2 cases, in both of which an unusual amount of bank blood had been given during the postoperative period because of surgical difficulties in securing adequate hæmostasis.

Plasma-hæmoglobin levels over 50 mg. per 100 ml. were unusual with either machine. Nor in most cases, could changes be detected in clotting-times, prothrombin-times, prothrombin-consumptions, or thromboplastin-generations. In a few cases, more pronounced rises in plasma-hæmoglobin, and definite changes in plasma-coagulation factors (especially those involved in the first stage of coagulation), did occur. These changes were correlated with the length of the bypass—and particularly with the amount of blood returned to the machine by suction from the interior of the heart—not with the type of machine used.

In no cases did a postoperative coagulation defect become a serious problem in management Proper heparin neutralisation was ensured by a protamine titration technique (Perkins et al 1956) Defects in plasma-coagulation factors (manifest most commonly by defective prothrombin-consumption) proved to be spontaneously reversible in a few hours, requiring no therapy beyond replacement of blood as it was lost In cases requiring more than the average amount of blood postoperatively, persistent thrombocytopenia was prevented by using fresh plastic bag or siliconed bottle blood (Jackson et al 1956)

Electrolyte Balance

We have noted only minor changes in the serum-electrolytes and have not regarded these as significant Although a slight acidosis and lowering of the carbon-dioxide content has been observed in the postoperative period, it has only very rarely needed correction A slight increase in the lactic-acid content of the blood has also occasionally been found, but this can be accounted for by accumulation of lactic acid in the blood used to charge the machines

Conclusions

Few surgical groups have had the opportunity of comparing two heart-lung machines used concurrently in clinical practice At Stanford University Hospital such a comparison has underlined not the differences but the similarities between two machines very different in design Each is capable of imitating closely the normal cardiac output and of providing adequate gas exchange even for a large man Neither has occasioned significant alterations in either the chemistry or the constituents of the blood and no untoward coagulation difficulties attend their use As an outcome of this comparison it has become possible to decide on one machine, and, for reasons of convenience, cost, and ease of management, an apparatus utilising modified Melrose rotating-disc oxygenator is to be substituted for the present instruments

Our experience lends support to the view that to improve the outlook for open heart surgery, improvement in team skill is more important than improvement in mechanical design Until a disposable closed-circuit pump oxygenator of membrane type has been fully tested and has been proved to have the outstanding advantages it promises, present requirements can be adequately met with existing machines We are convinced, however, that the most satisfactory clinical course follows the perfusion that most nearly maintains homœostasis, and that the machine chosen should be able to do this in all circumstances

A remarkable benign and uneventful postoperative picture is presented by most of those now undergoing such surgery The use of the median stenotomy incision rather than a bilateral thoracotomy decreases operating time considerably, and it is rare indeed for such a case to take more than three hours This reduction in operating time has proved as beneficial in intracardiac surgery as in any other branch

REFERENCES

Gerbode, F , Braimbridge, M , Melrose, D G (1958) *Arch Surg* 76, 821
— Melrose, D G (1958) *Amer J Surg* (in the press)
Gibbon, J H , Jr (1954) *Minn Med* 37, 171
Jackson, D P , Krevans, J R , Conely, C L (1956) *Trans Assoc Amer Phy* 69, 155
Kirklin, J W , McGoon, D C , Patrick, R T , Theye, R A (1958) Extracorporeal Circulation, p 125 Springfield, Ill
Melrose, D G (1955) *J Physiol* 127, 51P
— Dreyer, B , Bentall, H H , Baker, J B E (1955) *Lancet*, ii, 21
Osborn, J J , Gerbode, F , Perkins, H A , Kahn, P , Braimbridge, M (1957) *Trans Amer Soc art Intern Organs*, 3, 49
— MacKenzie, R , Shaw, A , Perkins, H A , Hurt, R , Gerbode, F (1956) *Surg Forum* 6, 96
Perkins, H A , Osborne, J J , Hurt, R , Gerbode, F (1956) *J Lab clin Med* 48, 223

TOBACCO AMBLYOPIA: A CLINICAL MANIFESTATION OF VITAMIN-B_{12} DEFICIENCY

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SINCE tobacco amblyopia was first described by Beer (1817) there has been much discussion about its ætiology By definition tobacco is a necessary factor, but why should only a few people who smoke get this amblyopia? We attempt to answer this question

Tobacco amblyopia is commonest in middle-aged males Traquair (1930) found extremes of 23 and 84 years and only 7 females in 1525 cases The amount of tobacco smoked varies considerably Usher (1927) and Traquair (1930) found an average weekly consumption of 3 oz, with extremes of $^1/_2$ oz and 9 oz Tobacco amblyopia usually affects persons who smoke strong pipe tobacco, cigars and cigarettes are seldom responsible. Most patients have smoked for many years Nettleship (1887) found symptoms developing after a minimum of a year's smoking

It is generally accepted that excessive consumption of alcohol tends to increase the incidence and severity of tobacco amblyopia

Many workers have recognised the importance of the nutrition and general health of the patient (Mackenzie 1854, Traquair 1930, Greeves 1946, Evans 1946, Schepens 1946) It has been suggested that a deficiency of one or more members of the vitamin-B group may be an ætiological factor, and the response to vitamin-B complex and yeast has been studied (Shattuck 1928, Minot 1929, Carroll 1944), but these clinical trials have not convincingly shown that it is deficiency of vitamin-B complex that is the cause of tobacco amblyopia In many cases smoking had been stopped, this alone improves most cases Often the diet and drinking habits of the patients had been altered, and it is now known that yeast contains a small quantity of vitamin B_{12} (Peeler et al 1951)

Duke-Elder (1954) noted that the injection of large doses of vitamin B_{12} was effective in tobacco amblyopia, even if smoking was continued It was therefore decided to determine whether tobacco amblyopia could be regarded as one of the clinical manifestations of vitamin-B_{12} deficiency

Method

In this series the criteria on which the diagnosis of tobacco amblyopia was based were as follows

(1) The patient must be a smoker

(2) A centrocæcal scotoma must be present

(3) This scotoma must be horizontally oval, with a sloping edge and most easily detected by a reduced stimulus—i e , with a red or a small white test object

(4) The scotoma must be bilateral, though not necessarily equal on the two sides

(5) The defect for colour must exceed that for white

(6) There must be definite nuclei within that scotoma on the horizontal meridian

(7) An impairment of the temporal colour field must exist within the 30° circle (In the more advanced cases a similar defect is also seen to a small white test object)

The visual fields were investigated by one of us only (A J A M) to ensure uniformity of technique

During a twelve-month period 14 male patients with tobacco amblyopia were seen by us at the Bristol Eye Hospital A history was taken from each patient and a complete clinical examination made In addition each patient underwent a full blood examination, gastric analysis, liver-function tests, and measurement of the serum-vitamin-B_{12} level It was also decided that biopsy of the sternal marrow should be undertaken in every patient with histamine-fast achlorhydria and evidence of neurological involvement, irrespective of whether or not anæmia was present

A summary of the clinical and pathological findings in 14 cases of tobacco amblyopia and the response to treatment with cyanocobalamin is included in the accompanying table

Results

Anæmia

The hæmoglobin level was less than 90% in 3 of the 14 patients with tobacco amblyopia

2 of these patients (cases 1 and 2) had histamine-fast achlorhydria and a megaloblastic marrow and therefore could be described as having the retrobulbar neuritis of addisonian pernicious anæmia

Case 1—A man, aged 62, was initially seen at the Bristol Eye Hospital in June, 1956, with three months' history of failing vision His visual acuity was right 6/24, left 6/18, and the fields were typical of tobacco amblyopia He was advised to stop smoking immediately and was given oral vitamin B_1 In spite of this his vision slowly deteriorated

CLINICAL AND PATHOLOGICAL FEATURES IN 14 MEN WITH TOBACCO AMBLYOPIA

Case no	Age (yr)	History of smoking (yr)	Visual acuity		Histamine fast achlorhydria	Hb (%)	Blood-picture	Serum bilirubin (mg per 100 ml)	Glossitis	Neurological involvement *	Serum-vitamin-B_{12} level (µµg per ml)	Visual acuity after smoking stopped and oral vitamin-B complex given		Visual acuity after parenteral vitamin B_{12}		Remarks
			Rt	Lt.								Rt	Lt.	Rt	Lt	
1	62	35	6/24	6/18								6/60	2/60			Deterioration of visual acuity followed cessation of smoking and treatment with oral vitamin B_1
	63	36	6/60	2/60	No acid	86	Normocytic normochromic film, megaloblastic marrow	0·2	–	+	15			6/9	6/9	After 5 mos treatment with parenteral vitamin B_{12}, the fields, which were typical of tobacco amblyopia, including the nuclei, had almost returned to normal
2	75	—	6/6	6/6	No acid	33	Megaloblastic	0·7	—	—						Treated with anahæmin
	77	1½	6/60	6/60		93	Normal peripheral blood		—	—	130			6/12	6/9	Visual acuity and fields much improved after treatment with vitamin B_{12} for 2 mos
3	81	50+	6/24	6/18	Free acid	89	Normocytic normochromic film, normoblastic marrow	2·75	–	+	300			6/9	6/9	Continued smoking, fields reverted to normal in 2 mos
4	66	50	6/60	6/24	Refused gastric analysis	110	Normal film (refused marrow biopsy)	0·9	—	+	230			Failed to attend		—
5	78	60	6/9	6/24	Free acid	102	Normal	0·45	—	+	330	6/9	6/24	6/9	6/24	Choroidal sclerosis, field typical of tobacco amblyopia Reverted to normal after treatment with B_{12}
6	52	30	6/36	6/36	Free acid	112	Normal	1·8	—	+	15	6/9	6/6	6/6	6/6	On vitamin-B complex and stopped smoking for 14 mos, yet right field still showed centrocæcal scotoma to red, fields reverted to normal after 2 mos treatment with vitamin B_{12}
7	65	50+	6/60	2/60	No acid	96	Normal	0·6†	+	—	220	6/24	2/60	6/12	6/24	Senile cataracts, stopped smoking and took vitamin-B complex for 17 mos, yet still tobacco amblyopia After 4 mos treatment with vitamin B_{12} fields were normal in both eyes
8	72	55	3/60	2/60	No acid	114	Normal	0·95	+	—	300	6/60	6/60	6/9	6/9	Stopped smoking and took vitamin-B complex for 4 mos fields normal after treatment with vitamin B_{12} for 3 mos
9	64	50	6/24	6/24	No acid	113	Normal	0·4	—	—	350	6/6	6/9	Not given		Rt field normal Lt field small centrocæcal scotoma to red 10 mos after stopping smoking
10	66	45	6/9	6/24	No acid	107	Normal	0·35	—	—	220	6/9	6/12	6/6	6/9	Continued smoking with treatment, fields improved after 2 mos treatment with vitamin B_{12}
11	76	66	6/18	6/6	No acid	94	Normal	0·7	—	—	230	6/5	6/5	Not given		Fields normal 3 mos after stopping smoking
12	60	40	6/18	6/9	No acid	99	Normal	0·65	—	—	200	6/6	6/6	Not given		Fields normal 6 mos after stopping smoking
13	47	30	6/60	6/6	Free acid	96	Normal	0·45	—	—	300	6/6	6/5	Not given		Small centrocæcal scotomata to red in both eyes 4 mos after stopping smoking
14	67	50+	6/60	Hand movements only	Free acid	104	Normal	1·35	—	—	Not done			6/36	Hand movements only	Stopped smoking and given vitamin B_{12}, visual fields returned to normal in 2 mos, advanced senile cataracts

* Neurological involvement, see text for full details

† Serum-alkaline-phosphatase 16 King-Armstrong units per 100 ml, serum-globulin 3·3 g per 100 ml

In March, 1957, he was admitted with three months' history of soreness of the tongue, slurring of speech, and numbness and paræsthesiæ in both legs. His visual acuity was right 6/60, left 2/60. The fields were now difficult to map accurately owing to poor fixation but showed a large centrocæcal scotoma to 3/1000 white on the right and to 15/1000 white on the left, with gross depression of the temporal fields to 15/1000 red. The tongue was smooth and red at the edges. There was impaired sensation to pinprick in both legs below the knees and diminished sense of position and vibration in the feet.

The hæmoglobin level was 86%, the serum-vitamin-B_{12} level was 15 μμg per ml. Parenteral administration of cyanocobalamin 100 μg daily for fourteen days followed by 100 μg twice a week produced a dramatic improvement in the vision. Two months after treatment had been started the visual acuity was right 6/24, left 6/12, and the patient now had classical tobacco-amblyopia fields. His vision in both eyes improved to 6/12 in three months and 6/9 in six months.

Comment.—It seems reasonable to suggest that the tobacco amblyopia in case 1 can be regarded as a clinical manifestation of vitamin-B_{12} deficiency. The deterioration of vision and the defect in the visual field preceded the onset of anæmia, glossitis, and neurological involvement by more than nine months. The excellent response to parenteral vitamin B_{12} further supports the view that a combination of the toxic effect of tobacco on the retina and the low serum-vitamin-B_{12} level produced tobacco amblyopia.

Case 2.—A man, aged 75, was admitted to Southmead Hospital in August, 1956, under the care of Dr. J. A. Birrell with pernicious anæmia. He was treated with 'Anahæmin', and on discharge his hæmoglobin had increased from 33 to 70%.

In February, 1958, he attended the Bristol Eye Hospital with four weeks' history of failing vision. He had started smoking a pipe sixteen months previously. His visual acuity was 6/60 in each eye, and he had tobacco-amblyopia fields. No other abnormal physical signs were present. For the past eighteen months he had been having anahæmin 2 ml. twice weekly. His hæmoglobin level was now 93% and serum-vitamin-B_{12} level 130 μμg per ml. He was given parenteral cyanocobalamin 100 μμg twice weekly and allowed to continue smoking; within two months his vision had improved to right 6/12, left 6/9.

Comment.—It is evident that, in this known case of treated pernicious anæmia, vitamin-B_{12} deficiency was not sufficient to produce anæmia or signs of peripheral neuropathy or spinal-cord involvement. However, as in case 1, it seems reasonable to presume that the retina had been made unduly sensitive to vitamin-B_{12} deficiency. This hypothesis is supported by the knowledge that there was no amblyopia when the patient was very anæmic (Hb 33%), and at that time he was a non-smoker.

In case 3 neurological features suggesting vitamin-B_{12} deficiency were present, but there was free acid in the gastric juice, biopsy of the marrow showed normoblastic erythropoiesis, and there was biochemical evidence of liver dysfunction.

Case 3.—A man, aged 81, had six months' history of progressive deterioration of vision. For about two months he had had a sore tongue, numbness and tingling in his hands and feet, weakness of his legs, and difficulty in walking.

On examination his visual acuity was right 6/24, left 6/18, and the fields were typical of tobacco amblyopia. His tongue was red and smooth. His gait was a little unsteady. He had a definitely weak grip and some loss of power in both legs. Stocking anæsthesia to light touch and pinprick was present in both legs below the knees, and their sense of position and vibration was impaired. The knee-jerks were diminished, the ankle-jerks absent, and the plantar responses flexor. The hæmoglobin was 89%. A blood-film showed normocytic normochromic blood with anisocytosis and poikilocytosis. Gastric analysis revealed free acid, and the marrow was normoblastic. The serum-bilirubin level was 2.75 mg. per 100 ml. and the serum-vitamin-B_{12} level 300 μμg per ml. The Wassermann reaction was negative.

Comment.—Case 3 had clinical manifestations of vitamin-B_{12} deficiency: glossitis, peripheral neuropathy, and involvement of the posterior spinal column. Within two months of parenteral administration of cyanocobalamin the visual acuity had improved to 6/9 in both eyes and the fields had become normal. This dramatic response can be entirely attributed to cyanocobalamin because the patient continued to smoke as heavily as before throughout the course of treatment.

Neurological Involvement

Clinical evidence of peripheral neuropathy, spinal-cord involvement, or encephalopathy was present in 5 of the 14 cases. Case 1 had pernicious anæmia. In case 4 the clinical picture strongly suggested subacute combined degeneration of the cord, but unfortunately the patient refused permission for full investigation and has repeatedly failed to attend for follow-up examination.

In the remaining 3 patients with neurological features suggesting vitamin-B_{12} deficiency gastric analysis revealed free acid. The findings of peripheral neuropathy and involvement of the posterior column in case 3 have already been reviewed. In case 5 there was six months' history of paræsthesiæ in both legs below the knees, but no abnormal signs were detected. The presentation of tobacco amblyopia and mental changes (acute depression, irritability, and failing memory for two months) in a non-anæmic patient (case 6) is of particular interest. Although free acid was present in the gastric juice, the serum-vitamin-B_{12} level was exceptionally low (15 μμg per ml.) and liver-function tests showed a raised serum-bilirubin level.

Glossitis

A sore red smooth tongue was observed in 4 of our 14 patients. In 2 of these 4 the hæmoglobin level was below 90%; case 1 had pernicious anæmia, and case 3 had free acid and a normoblastic marrow. The 2 non-anæmic patients were forbidden to smoke and were initially given oral vitamin-B complex. This regime apparently produced no improvement in the state of the tongue. Treatment with cyanocobalamin caused complete subjective and objective improvement in the glossitis in all 4 patients.

Serum-vitamin-B_{12} Levels

The serum-vitamin-B_{12} levels were estimated by microbiological assay with *Euglena gracilis* var. *bacillaris* as test organism (Mollin and Ross 1952, 1954). With this method Mollin and Ross found that the normal range for serum-vitamin-B_{12} levels was 100–900 μμg per ml., with a mean value of 360 μμg per ml. The levels obtained in our patients with tobacco amblyopia were compared with those of a control group of healthy persons matched for sex and age.

In 13 patients with tobacco amblyopia the serum-vitamin-B_{12} levels ranged from 15 to 350 μμg per ml., with a mean value of 218 μμg per ml. The values for 12 controls ranged from 280 to 1000 μμg per ml., with a mean value of 538 μμg per ml. The difference in the serum-vitamin-B_{12} levels between the patients and the controls appears highly significant ($P<0.01$), according to the distribution-free type of test function used (the X-test by Van der Waerden). There is no significant difference in age between the two groups by the same test function.

Treatment with Cyanocobalamin

Most cases of tobacco amblyopia improve when the patient stops smoking, and many cases even when smoking is only reduced. In our series cases 11 and 12 were completely cured in this way, and 4 patients cases (6, 9, 10, and 13) were clinically cured although slight signs of tobacco amblyopia remained in their fields.

This method of treatment has disadvantages: it is irksome to the patient, and the recovery-rate varies. In 170 cases Griffith (1887) found an average recovery period of seventeen months, with extremes of three and forty-two months. In our small series case 11 recovered in three months, whereas case 7 had not recovered after seventeen months. Rarely the vision may deteriorate, as in case 1 and in 4% of Griffith's (1887) cases.

We gave cyanocobalamin to 9 patients, of whom 3 continued smoking as heavily as before. All recovered more rapidly than would have been expected with the prohibition of smoking and oral vitamin-B complex alone, 6 patients had initially had this orthodox treatment. Parenteral cyanocobalamin 100 μg. was first given once or twice weekly for a month (once a day for the first fourteen days to our anæmic patients), then every fortnight for two months, and finally at intervals of a month. Probably it is safe to stop treatment after six months, provided that the fields are normal and there is no evidence of addisonian pernicious anæmia or neurological involvement. Our experience in this clinical trial suggests that much larger doses of cyanocobalamin would have been even more rapidly effective.

Discussion

Tobacco Amblyopia, Vitamin-B$_{12}$ Deficiency, and Histamine-fast Achlorhydria

Gastric analysis revealed histamine-fast achlorhydria in 9 of 15 patients with tobacco amblyopia described by Leishman (1952) and in 8 of 13 cases in the present survey. In these 8 cases the serum-vitamin-B$_{12}$ levels ranged from 15 to 350 μμg. per ml., with a mean value of 208 μμg. per ml.

Histamine-fast achlorhydria is an essential feature of addisonian pernicious anæmia and may precede the onset of anæmia by many years (Hurst 1922, Meulengracht 1925). Callender and Denborough (1957) produce evidence that there is a "pre-pernicious-anæmia" state in which there is achlorhydria with gastric atrophy, poor absorption of vitamin B$_{12}$ corrected by intrinsic factor, and a low or a low normal serum-vitamin-B$_{12}$ level without symptoms of anæmia. 2 of Leishman's (1952) patients and 1 of ours (case 1) developed tobacco amblyopia many months before they were found to have pernicious anæmia. In view of this it seems likely that they were in the "pre-pernicious anæmia" state at the time. One of the manifestations of this state might therefore be tobacco amblyopia. Callender and Denborough refer to the inheritance of pernicious anæmia and the "pre-pernicious-anæmia" state. Nettleship suggested that tobacco amblyopia might have a genetic basis.

Mollin and Ross (1954) have shown that a critical level for vitamin-B$_{12}$ deficiency is 100 μμg. per ml., and that above this level in the serum the marrow is normoblastic. Because a level of 100 μμg. per ml. is a critical level for the marrow, it does not necessarily follow that the same applies to the retina poisoned by tobacco. It may well be that about 250 μμg. per ml. is the critical level of serum-vitamin-B$_{12}$ for the development of tobacco amblyopia. The level of free vitamin B$_{12}$ in the serum might also be important in this context because presumably it is only the free vitamin B$_{12}$ that can be immediately used by the retina. Unfortunately we could only estimate the level of total vitamin-B$_{12}$ in the serum.

In view of the fact that 2 of our patients (cases 1 and 2) with tobacco amblyopia and 10 of 75 cases reviewed by Leishman (1952) were found to have pernicious anæmia, we decided to review the published cases of retrobulbar neuritis in pernicious anæmia (Cohen 1936, Box 1936, Hine 1936, Talbot 1936, Kampmeier and Jones 1938, Turner 1940, Benham 1951, Nelson and Weaver 1956).

A survey of these case-reports suggests that many of these patients with pernicious anæmia could be described as having tobacco amblyopia. Of 15 patients 9 were specifically reported as being smokers and 14 were males, yet the proportion of males to females in pernicious anæmia is usually given as 1 : 3. One of the characteristics of British and American males is that they tend to smoke pipes and cigarettes more than do females. Unfortunately most of the fields reported were incomplete, the central fields were not always recorded, and only Benham (1951) used a red object. However, centrocæcal scotomata were found in 6 cases, which suggests tobacco amblyopia. Turner (1940) noted that the development of amblyopia was not related to the degree of anæmia or to neurological involvement. Possibly it is related to the smoking habits of the patient, the retina being unduly sensitive to tobacco owing to vitamin-B$_{12}$ deficiency. In retrobulbar neuritis of pernicious anæmia the histological findings in the optic nerves (Bickel 1914) appear to be similar to those observed in tobacco amblyopia (Duke-Elder 1954).

Vitamin-B$_{12}$ Deficiency in Liver Dysfunction

Since free acid was present in the gastric juice in 5 of 13 patients with tobacco amblyopia in our series and in 9 of 15 patients in Leishman's (1952) series, it is evident that addisonian pernicious anæmia or the "pre-pernicious-anæmia" state cannot be regarded as the only condition predisposing to the development of tobacco amblyopia.

In our 14 cases there was no history or clinical evidence of liver disease in any patient. However, it is well known that portal cirrhosis may remain latent for many years, and that its incidence increases with age. Rolleston and McNee (1929) and McCartney (1933) reported that 52·1% and 35% of cases of cirrhosis of the liver found at necropsy had no history, symptoms, or signs of liver disease during life. In this clinically latent group even liver-function tests may be completely normal (Hetzel 1950).

In 6 of the 14 patients with tobacco amblyopia liver-function tests indicated some abnormality. There was a slight increase in the serum-globulin and serum-alkaline-phosphatase levels in 1 patient and a raised serum-bilirubin level in 5 patients. If the normal serum-bilirubin level is accepted as being 0·62 ± 0·25 mg. per 100 ml. (Schilling and Harris 1952), the serum-bilirubin levels were high in 5 cases (2·75, 1·8, 1·35, 0·95, and 0·9 mg. per 100 ml.). Both De Schweinitz and Edsall (1903) and Greeves (1946) also found evidence of liver dysfunction in some of their patients with tobacco amblyopia. In our two proved cases of addisonian pernicious anæmia the liver-function tests were normal, and similar findings were reported in 19 of 20 patients with untreated pernicious anæmia described by Schilling and Harris (1952).

Swendseid et al (1957) found that, in cirrhosis, there is a greatly reduced level of vitamin B_{12} in the liver, the average value being 26 µg per 100 g, whereas in healthy people of all age-groups there is an average of 70 µg per 100 g. of wet tissues Probably, therefore, in some cases of tobacco amblyopia there is a low level of vitamin B_{12} in the liver

Vitamin B_{12} exists in the serum both free (when it can be utilised by the tissues) and bound to α-globulin It has been shown (Lear et al 1954, Jones and Mills 1955, Rachmilewitz et al 1956, Mackay et al 1957) that, in hepatic cirrhosis, there is a rise in the level of bound vitamin B_{12} and often a fall in that of free vitamin B_{12} in the serum and an increased urinary excretion of what is apparently free vitamin B_{12} In a case of obstructive hepatic necrosis described by Mackay et al (1957) very high levels of bound vitamin B_{12} were found in the serum It is suggested that, in some cases, the liver releases a binding protein with a high avidity for vitamin B_{12} which would "mop up" any available free vitamin B_{12} and hold it in the blood-stream If this were so, we suggest that there might be less free vitamin B_{12} available to the retina and hence, if the patient was a heavy cigarette smoker or a pipe smoker, an increased liability to tobacco amblyopia

In view of these findings and suggestions it is unfortunate that the levels of free vitamin B_{12} in the serum of our patients with tobacco amblyopia could not be measured In our 6 patients with abnormal liver-function tests the levels of total vitamin B_{12} in the serum ranged from 15 to 300 µµg per ml, with a mean value of 213 µµg The mean value in our healthy controls was 538 µµg per ml

Low Serum-vitamin-B_{12} Levels in Dietary Deficiency

It is well recognised that the serum-vitamin-B_{12} levels may be very low after partial or total gastrectomy and in association with the "blind loop" and malabsorption syndromes, diverticulosis of the small intestine, and treatment with anticonvulsants (Spray and Witts 1958) Friedenwald (1953) has also shown that diabetics have a tendency to vitamin-B_{12} deficiency, this then may explain the increased incidence of tobacco amblyopia in diabetics Low serum-vitamin-B_{12} levels have also been reported in "vegans" who cannot absorb normal amounts of this vitamin Badenoch (1954), Harrison et al (1956), and Spray and Witts (1958) have described megaloblastic anæmia due to dietary deficiencies A dietary deficiency of vitamin B_{12} may be present in some elderly men, particularly if they live alone This deficiency might be expected to predispose towards the development of tobacco amblyopia long before producing megaloblastic anæmia or evidence of neurological involvement The increased severity and frequency of tobacco amblyopia which Schepens (1946) found among mal-nourished Belgians could be explained in this way Some of the complicated changes in the visual field of prisoners-of-war in the Far East may be due to a combined deficiency of vitamin B_1 and vitamin B_{12}, the former causing the central, and the latter, combined with smoking, causing the centrocæcal part of the scotoma (Livingston et al 1946)

Conclusions

We have presented evidence that, in persons with even mild vitamin-B_{12} deficiency, the retina or the optic nerve is unduly sensitive to tobacco

In a study of 13 patients with tobacco amblyopia the vitamin-B_{12} levels in the serum ranged from 15 to 350 µµg per ml These values differed significantly from those obtained in healthy controls, the mean level in our patients being 218 µµg per ml and that in the controls 538 µµg per ml

Other clinical manifestations of vitamin-B_{12} deficiency may be absent because, in pipe smokers and in heavy smokers of cigarettes, the amblyopia may precede the onset of anæmia, glossitis, neurological involvement, or megaloblastic bone-marrow by months or even years

We have also produced evidence that tobacco amblyopia and the retrobulbar neuritis of addisonian pernicious anæmia may be one and the same condition

An important additional finding is that, in 2 of our patients, tobacco amblyopia and neurological features suggesting vitamin-B_{12} deficiency were associated with free acid in the gastric juice, abnormal liver-function tests, and low serum-vitamin-B_{12} levels

We therefore suggest that, in any case of unexplained peripheral neuropathy, myelopathy, or encephalopathy, especially if it is considered to be due to nutritional deficiency, the levels of total and of free vitamin-B_{12} in the serum should be measured, even if histamine-fast achlorhydria is not present

Gastric analysis revealed free acid in 5 of 13 patients, and in 6 of 14 there was biochemical evidence of liver dysfunction

In this limited clinical trial the effect of parenteral cyanocobalamin in improving visual acuity and completely reversing the changes in the visual field has been most encouraging, even if the use of tobacco is continued

We thank the consultants of the Bristol Eye Hospital for permission to study and treat their patients, Miss A Sinclair Rose, of the Public Analyst's Department, Canynge Hall, Bristol, for the microbiological assays, Dr G Herdan for the statistical analysis of our results, Mr F C E Rooke, charge-nurse, for help, and Dr C C Ewing for criticism

REFERENCES

Badenoch, J (1954) *Proc R Soc Med* 47, 426
Beer, G J (1817) Lehre von den Augenkrankheiten, vol II Vienna
Benham, G H H (1951) *J Neurol Psychiat* 14, 40
Bickel, H (1914) *Arch f Psychiat, Berl* 53, 1106
Box, C R (1936) *Lancet*, ii, 1269
Callender, S T, Denborough, M A (1957) *Brit J Hæmat* 3, 88
Carroll, F D (1944) *Amer J Ophthal* 27, 713
Cohen, H (1936) *Lancet*, ii, 1202
De Schweinitz, G E, Edsall, D L (1903) *Trans Amer Ophthal Soc* 10, 41
Duke-Elder, W S D (1954) A Textbook of Ophthalmology, vol VI, p 6838 London
Evans, P J (1946) *Trans ophthal Soc U K* 66, 397
Friedenwald, J S (1953) *Amer J Ophthal* 32, 995
Greeves, R A (1946) *Trans ophthal Soc U K* 66, 446
Griffith, A H (1887) *ibid* 7, 81
Harrison, R. J, Booth, C C, Mollin, D L (1956) *Lancet*, i, 727
Hetzel, B S (1950) *Med J Aust* i, 1
Hine, M L (1936) *Proc R Soc Med* 29, 386
Hurst, A. F (1922) *Brit med J* ii, 978
Jones, P N, Mills, E H (1955) *J Lab clin Med* 46, 927
Kampmeier, R H, Jones, E (1938) *Amer J med Sci* 195, 633
Lear, A A, Harris, J W, Castle, W B, Fleming, E M (1954) *J Lab clin Med* 44, 715
Leishman, R (1952) *Trans ophthal Soc U K* 71, 319
Livingston, P C, et al (1946) *ibid* 66, 19
Mackay, I R, Cowling, D C, Gray, A (1957) *Brit med J* ii, 800
Mackenzie, W (1854) A Practical Treatise on the Diseases of the Eye London
McCartney, J S (1933) *Arch Path* 16, 817
Meulengracht, E (1925) *Amer J med Sci* 169, 177
Minot, G R (1929) *Ann intern Med* 3, 216
Mollin, D L, Ross, G I M (1952) *J clin Path* 5, 129
— — (1954) *Proc R Soc Med* 47, 428
Nelson, M G, Weaver, J A (1956) *Irish J med Sci*, p 229
Nettleship, E (1887) *Trans ophthal Soc U K* 7, 36
Peeler, H T, Yacowitz, H, Carlson, C W, Miller, R F, Norris, L C, Heuser, G F (1951) *J Nutr* 43, 49
Rachmilewitz, M, Aronovitch, J, Grossowicz N (1956) *J Lab clin Med* 48, 339
Rolleston, H D, McNee, J W (1929) Diseases of the Liver, Gall bladder, and Bile-ducts London
Schepens, C L (1946) *Trans ophthal Soc U K* 66, 309
Schilling, R. F, Harris, J W (1952) *J Lab clin Med* 40, 718
Shattuck, G C (1928) *Amer J trop Med* 8, 539
Spray, G H, Witts, L J (1958) *Brit med J* i, 295
Swendseid, M E, Hvolboll, E, Schick, G, Halsted, J A (1957) *Blood*, 12, 24
Talbot, G (1936) *Brit J Ophthal* 20, 619
Traquair, H M (1930) *Trans ophthal Soc U K* 1, 351
Turner, J W A (1940) *Brain*, 63, 225
Usher, C H (1927) *Ann Eugen, Lond* 2, 245

MALIGNANT RENAL HYPERTENSION (WILSON-BYROM SYNDROME) CURED BY NEPHRECTOMY

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It was predicted by Goldblatt (1948) that there would be many mistakes in the application to man of his classical experiments on renal hypertension in rats He did not mean that constriction of a main renal artery was the cause of all hypertension in man but that the experimental application of his clamp would exactly reproduce the physiological state of the kidney in essential hypertension He considered his experimental method to be the best suited to effect a state of abnormal physiology analogous to that caused by arteriolar sclerosis in the kidney—namely, reduction of intraglomerular capillary pressure and reduction of blood-flow to the nephron

Wilson and Byrom (1939) described a type of malignant hypertension in rats that apparently had its origin in reduced renal blood-flow During the next fifteen years they retested their theory, received confirmation from Blacket and Sellers (1951), and outlined (Wilson 1953) a syndrome of hypertension in rats which has the following clinical and pathological features

(1) Hypertension is produced by artificial stenosis of the main renal artery to one kidney, the artery to the other kidney remaining intact

(2) Encephalopathy eventually develops, often without uræmia

(3) The resulting hypertension produces extrarenal vascular lesions closely resembling those seen in human malignant hypertension in all organs except the kidney supplied by the stenosed artery

(4) Prompt removal of the kidney made ischæmic by the stenosis usually relieves the hypertension and is followed by disappearance of the encephalopathy

(5) Histologically the excised kidney and its stenotic artery reveal no abnormality

We report the following case for several reasons the pathological findings responsible for the hypertension closely parallel Goldblatt's original experimental method, clinical and laboratory data were collected both before and after operation, and strong support is given to the suggestion that malignant hypertension may be due to renal factors

Case-report

A weaver, aged 56, was admitted to this hospital on March 5, 1954, with several months' history of hypertension His family doctor first diagnosed hypertension in June, 1953, when the patient's blood-pressure was 210/110 mm Hg and nothing abnormal was found in his urine Treatment with 'Metamine' (triethanolamine trinitrate biphosphate) was instituted A few weeks later the patient had an attack of epigastric pain, hæmatemesis, and bitemporal headache In December, 1954, his blood-pressure was 224/110 mm Hg, and rales heard in his chest suggested a low-grade pulmonary infection Albuminuria had also appeared Antibiotics and digitalis procured the patient some benefit

On admission to this hospital his blood-pressure was 216/130 mm Hg in his right arm and 260/160 mm Hg in his left His cervical veins were distended He had a conjunctival hæmorrhage, grade-IV retinopathy, papillœdema, and flame-shaped retinal hæmorrhages His vision was much impaired. His heart was enlarged to percussion, and the edge of his liver was tender and palpable 8 cm below his costal margin His peripheral pulses were strong His lungs were emphysematous but free from rales

Investigation showed hæmoglobin 12 g per 100 ml, white blood-cells 15,300 per c mm, erythrocyte-sedimentation rate 28 mm in 1st hour (Westergren) and urine sp gr 1 029, copious albumin, blood-urea nitrogen 22 mg per 100 ml The phenolsulphonphthalein test showed that 10% of the dye was excreted in the first 15 minutes and 25% after 2 hours The retention of bromsulphalein was 20% Radiography of the chest showed that the heart was enlarged transversely with prominence of the left ventricle and calcification of the aortic knob The vascular markings of the lungs were consistent with early pulmonary congestion Intravenous pyelography showed an enlarged right kidney with good concentration of the dye, whereas the left kidney could not be seen at all There was calcification of the abdominal aorta and the iliac vessels Electrocardiography showed left ventricular strain Retrograde pyelography showed normal renal architecture bilaterally, but indigo-carmine injected intravenously was not excreted from the left kidney The arm-to-tongue circulation-time was prolonged by 31 seconds Lumbar puncture produced cerebrospinal fluid (C S F) under a pressure of 216 mm H_2O and containing protein 150 mg per 100 ml 'Regitine' reduced the blood-pressure from 254/150 to 210/110 mm Hg

Treatment and progress—Clinically the patient became rapidly worse while being observed under the customary treatment On the ninth day after admission his condition was desperate, and he lapsed into semicoma with Cheyne-Stokes respiration Lumbar puncture produced C S F under a pressure of 340 mm H_2O, and the electroencephalogram was very abnormal 50% glucose intravenously, hexamethonium, and hydrallazine were administered to improve his condition for surgery His blood-pressure fell from 254/150 to 220/110–120 mm Hg, the fall producing temporary improvement and mental clearing An attempt at retrograde aortography failed

Operation—On March 17, 1954, under spinal anæsthesia, left nephrectomy was done, with resection of a segment of the left renal artery At operation a pulseless renal artery and an apparently normal kidney confirmed the preoperative diagnosis of a Goldblatt kidney

Pathology—The operation specimen consisted of a section of stenosed renal artery, its lumen being reduced by 85% (fig 1), and the left kidney (118 g), whose capsule stripped easily The cortex measured 4 mm and the pyramids 11 mm The mucosa of the renal pelvis was slightly hæmorrhagic Microscopically the nephrovascular units were well preserved (fig 2), arteries and arterioles being normal Mild fibrous infiltration and lymphocytes were found in both the parenchyma and the capsule A few tubules were dilated with either hyaline or protein casts Microscopic sections of the

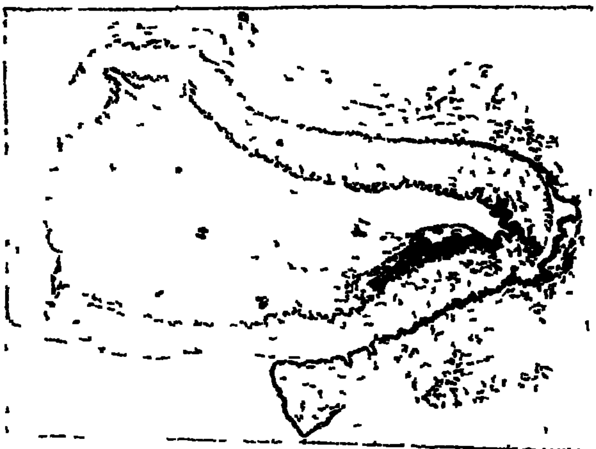

Fig 1—Cross-section of renal artery at site of maximal stenosis (Elastic-tissue stain)

renal artery showed extensive fibrous proliferation of the intima The elastic intima was distinct Occasional focal infiltration of lymphocytes in the proliferating intimal layer gave the picture of acute inflammation Unfortunately a biopsy specimen of the right kidney was not available to confirm feature no 3 of the syndrome (see above) We believe that this case satisfies the criteria outlined by Homer Smith (1948) for cure of hypertension by nephrectomy

Postoperative course—Striking changes followed surgery At the beginning of the operation the patient's blood-pressure was 250/150 mm Hg, and at its end 210/110 mm Hg By 10 P M that evening it was 154/90 mm Hg and by midnight 100/70 mm Hg When the electrocardiogram suggested myocardial ischæmia, noradrenaline was started by intravenous drip, and the blood-pressure rose to 180/100 mm Hg By March 24, five days after nephrectomy, the blood-pressure became steady at about 160/80 mm Hg There was never any evidence of surgical shock By March 27 there had been spectacular improvement in the visual acuity of the left eye, and the papillœdema in the right eye had disappeared The ophthalmologist considered the retinopathy to be grade IV on April 2, with corrected vision of 20/60 O D , 20/20 O S , and the capacity to read Jaeger-3 print A week later the corrected vision was 20/20 O U , and the patient could read Jaeger-1 Retinopathy was estimated at grade II on April 23 Lumbar puncture eleven days after the operation produced C S F under a pressure of 100 mm H_2O and containing protein 14 mg per 100 ml , compared with 340 mm H_2O and 150 mg per 100 ml preoperatively By April 21 the urine contained no albumin The blood-urea nitrogen was 26 mg per 100 ml four days before the operation, 17 mg per 100 ml by June, and 12 mg per 100 ml in December, 1954, and the urinary excretion of phenolsulphonphthalein had improved by August 24, 1954, to 40% in 15 minutes and 76% in 1 hour A bromsulphalein test on admission showed that 20% of the dye was retained, but on April 2, 1955, only 6% was retained The hæmoglobin increased to 14 6 g per 100 ml in August, 1954 On radiography the transverse diameter of the cardiac silhouette decreased to 143 mm by April 5, 1955, the radiological signs of pulmonary congestive completely disappeared, and electrocardiography showed less signs of left ventricular strain The preoperative electroencephalogram was interpreted as dysrhythmic, revealing many more frequencies of higher than average amplitude, especially in the frontal and central areas, these were described as consistent with disordered cerebral metabolism On Sept 14, 1955, electroencephalography showed remarkable improvement On admission the patient weighed 134 lb , and he claimed to have lost 40 lb in the preceding seven months By June, 1954, his weight had risen to 150 lb , and he said he had never felt better, being totally free from dyspnœa, palpitation, and headaches, and that his sight was constantly improving He was walking three or four miles daily During July, 1954, he drove his car 400 miles through Canada and then returned to his former job as a weaver in a textile mill, where he tends 52 looms

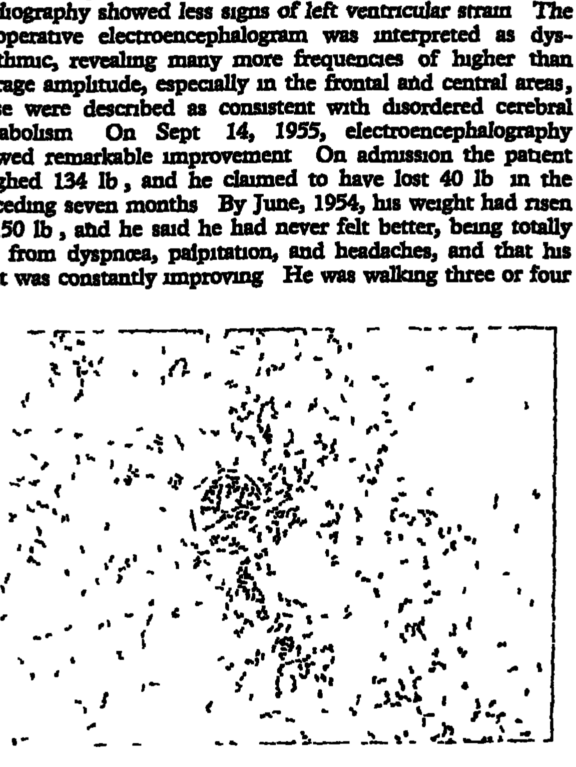

Fig 2—Random section from kidney, showing normal structure (Hæmatoxylin and eosin)

Follow-up—The patient was last studied in this hospital in December, 1957 (about four years after nephrectomy) For one and a half years after the operation he had remained in excellent general condition without medication of any kind and continued to maintain the striking improvement already described During the past year and a half, because his systolic blood-pressure had been found at times to be 180 mm Hg, his personal physician had treated him with hydrallazine rauwolfia ('Raudixin') At follow-up his blood-pressure was 166/80 mm Hg in the recumbent position and 140/70 mm Hg when he was standing Radiography of his chest showed the cardiac silhouette unchanged from two years ago, it remained slightly enlarged without signs of congestive failure An electrocardiogram was also identical with that of March, 1955 His urine contained no albumin, sugar, or pathological sediment His optic fundi were examined by the same ophthalmologist who had observed him before and after nephrectomy, no changes were found from their condition at September, 1955, and the patient's vision was O D 20/25, O S 20/30 (with glasses) The ophthalmologist's impression was grade-II hypertension, grade I/II arteriosclerosis The patient reported "feeling better than ever," sleeping soundly, and without headaches He walks daily about two miles without discomfort

Discussion

Experimental Background

In their original and subsequent investigations Wilson and Byrom used the Wistar strain of rats, which were prepared by applying an annealed silver ribbon clip to one of the main renal arteries after the method of Pickering and Prinzmetal (1938) In 65% of the rats so manipulated severe hypertension was produced in 1–28 days and lasted, in some rats, nine months The silver clip was applied so as to narrow the main renal artery without completely occluding its lumen, accomplishing the same thing technically and physiologically as the Goldblatt clamp Daniel et al (1954) have shown, by angiography, vasoconstriction of the intrarenal blood-vessels and parenchymal ischæmia within the "clipped" kidney in hypertensive rabbits Wilson and Byrom found in 77% of their rats malignant nephrosclerosis in the unclipped kidney and normal histology in the protected "clipped" kidney

Now Goldblatt, who failed to reproduce these findings in the dog and the sheep, considered that the characteristic malignant arteriolar lesions in the unclipped kidney of the rat could have been the result of pyelonephritis or of unrecognised disease in the clipped kidney Wilson (1953) then re-examined their material by using their control rats and concluded that their original interpretation of the renal lesions was correct and that the lesions were not the result of laboratory infections Confirmation of these unusual vascular findings by Daniel et al (1954) suggests strongly that the rat's kidney behaves more like the human kidney than like that of the dog Species differences are well known in laboratory investigations (Daniel et al 1952)

Wilson (1953) next made some experiments which even more closely incriminated the kidney in hypertension He noted that, if a rat was made hypertensive by the application of a clip to one main renal artery, excision of the contralateral unclipped kidney did not lower the blood-pressure, but, if the clip was removed to the main artery of the other kidney the blood-pressure usually dropped to normal

The foregoing experiments were made on rats with acute hypertension but subsequent experiments on rats with long-standing hypertension showed that, in chronic hypertension, simple removal of the clip often did not reverse the hypertension. Wilson (1953) considered that this was due to irreversible changes within the other kidney, which in time came to resemble the effect of a "clip" in producing renal ischæmia.

In further support of their theory they produced chronic hypertension by stenosis of one renal artery until the damage in the contralateral kidney was irreversible. The clip was then removed, and the hypertension persisted. Finally, the unclipped kidney with irreversible changes was removed from these rats with chronic persisting hypertension, and the blood-pressure promptly fell to normal. Such observations lend strong support to the renal genesis of this type of hypertension and of the malignant variety in particular.

Abeshouse (1941) reviewed the published cases and enumerated the underlying lesions, ranging from renal tuberculosis to renal aneurysms. However, at that time the significance of stenosis of the main renal artery as a cause of hypertension was not fully appreciated. In a complete review of the English and American published cases we have found 21 in which stenosis of the main renal artery of one kidney was considered to be the chief cause of the hypertension. All these cases have certain clinical and pathological features in common which imitate the experimental syndrome in rats. Although certain data are missing, one can justifiably presume what the completed picture would be and infer that these cases represent hypertension resulting from stenosis of a renal artery, with pathological changes reaching one of the several stages of the experimental syndrome.

In the 9 cases in which both kidneys were examined few if any pathological changes were reported in the kidney protected by the stenosis, whereas in the contralateral kidney were severe degenerative changes mainly resembling nephrosclerosis. This dissimilarity between the two kidneys is difficult to explain on a basis of chance findings. In the present case the renal histology was not remarkable in the excised kidney (which was protected by the stenosed artery in a manner comparable to the clipped kidney in the rat), but the changes in the arterioles of the ureter suggest that there may well have been vascular changes in the other kidney. In 14 of the 21 cases nephrectomy cured the hypertension. In 1 case the stenosis of the artery was alone corrected without removing the kidney, and normotension was restored. It is reasonable to suppose that some of the patients who died could have been saved by nephrectomy.

We must emphasise again that we have reviewed only those 21 cases in which a main renal artery to one kidney only was stenosed. In 1 case the stenosis was due to encroachment by a tumour, in 1 other it was caused by an aneurysm, and in the remaining 19 the artery was narrowed by an arteriosclerotic plaque (but histological proof was not always obtained). Although encephalopathy developed in 8 cases, 3 of these patients were still well at the end of two years, and in the remaining 5 cerebral changes were not mentioned, or else the disease had not progressed so far. Uræmia was an accompanying condition in only 3 of the 8 with encephalopathy. All 8 had severe hypertension, the lowest blood-pressure being 180/110 mm Hg. These observations show how closely human material, even in limited amount, fits the criteria which appear to be important in the experimental syndrome in rats.

In looking for published cases of stenosis of a main renal artery we found 20 other cases of hypertension thought to be the result of renal ischæmia but excluded them for various reasons (Bourne 1954, Masiloff and Macht 1951, Aronson and Sampson 1951, Perera and Haelig 1952, Fishberg 1941, Wainwright 1949, Hussar and Bernstein 1954, Prinzmetal et al. 1942, Howard et al. 1954, Blahd et al. 1952, Yuile 1944, Leiter 1938, Hoffman 1942, Perry 1945).

Diagnosis

Clinicians are cautious about diagnosing hypertension due to unilateral renal disease. The treatment implies nephrectomy, and past experience has shown that only a fifth of the unselected cases of hypertension and unilateral renal disease would be helped. However, if the syndrome accurately resembles that described here, the cure-rate will be very much higher.

The ideal candidate is a patient with severe hypertension (a raised diastolic blood-pressure of 110 mm Hg or higher) in whom the disease is rapidly progressing and more organs are becoming affected. The heart may exhibit severe electrocardiographic changes, left ventricular strain, and T-wave changes. Encephalopathy with coma, stupor, or convulsions may ensue. The signs may vary according to the duration and severity of the hypertension, but, if the changes are severe, there is all the more reason for considering the present syndrome, the severity of these changes should not contraindicate surgery. Intravenous and retrograde pyelography should aid in localising the disease, but their interpretation may be uncertain, as the 2 cases of Howard et al. (1954) showed. If there are electroencephalographic or other cerebral changes, lumbar puncture should be done to rule out arteriosclerotic encephalopathy. Pickering *et al.* (1952) observed that, when albuminuric retinitis is present, the pressure of the C.S.F. is nearly always above the level at which brain tumours cause papillœdema. In arteriosclerotic retinitis with encephalopathy the pressure of the C.S.F. is lower. The usual renal-function tests are not easy to assess, because apparently poor function can be reversed dramatically after nephrectomy. The regitine test is of no value, because it may be positive in the present syndrome and in the presence of uræmia, as is well known. If intravenous pyelography is not conclusive, aortography is of the greatest importance, as in the cases reported by Howard et al. (1954) and Freeman et al. (1954).

The ocular fundi should be carefully examined. The observation of Volhard and Fahr (1914) that the distinctive feature of malignant hypertension is albuminuric retinitis (hypertensive neuroretinopathy) still receives strong support. It is distinguished from arteriosclerotic retinitis by the presence of bilateral neuroretinal œdema, which is absent in arteriosclerotic retinitis except as a consequence of venous thrombosis.

Recent studies by Howard et al. (1956) indicate that there is a method of detecting the "endocrine" kidney when intravenous pyelography and/or aortography are negative: urine is collected from each kidney through retrograde catheters, and the amounts of sodium and chloride in it are measured. The endocrine or pathological kidney is detected by its decreased excretion of sodium and water.

Pathology

A study of 21 published cases selected as representing the syndrome produced experimentally in rats by Wilson and Byrom (1939) has brought forth very interesting facts. *In all* of them a renal artery was narrowed. Of the 11 surviving patients who underwent nephrectomy no histological data are available about the kidney which still remains in situ, but of the excised kidneys 7 had completely normal renal parenchyma, 3 had areas of tubular atrophy, and 1 had interstitial inflammation and fibrosis These latter abnormalities were not considered severe enough to cause the hypertension Of the 8 patients who died 7 at necropsy had malignant nephrosclerosis of the kidney whose artery was patent and only minor or indifferent changes in the kidney protected by the stenotic artery In Stewart's (1941) case there was parenchymal atrophy only on the side where the artery was fully patent, this case should therefore probably not be considered typical of the present syndrome, because it does not fulfil all the criteria Blackman (1939) found at necropsy narrowing of the renal artery in 43 of 50 cases of essential hypertension but only in 5 of 50 non-hypertensives Narrowing of the artery per se is therefore insufficient to diagnose the present syndrome, the diagnosis must rest on the complete clinicopathological picture The 2 cases reported by Thompson and Smithwick (1952) are exceptional in that, as a result of biopsy, definite dissimilarities between the affected and the "protected" intact kidneys of surviving patients were observed the pathological changes in the "protected" kidneys were minimal in contrast to those in the other kidneys with patent arteries This shows the value of renal biopsy as a guide to prognosis and diagnosis

Treatment

This syndrome has been alleviated surgically in various ways, but the series is too small for statistical analysis Of the 21 cases 11 were cured by nephrectomy In 1 case (Freeman et al 1954) relief of the stenosis of the renal artery lowered the blood-pressure In another case (Thompson and Smithwick 1952) removal of an aneurysm did not change the blood-pressure, but it is not stated whether the diameter of the artery had been changed, as was so well shown by aortography in the case of Freeman et al (1954) Goodman (1952) reported a case in which neither medical treatment nor bilateral lumbodorsal sympathectomy altered the course of the disease, which was fatal Thompson and Smithwick (1952) also noted failure of lumbodorsal sympathectomy to effect improvement

The importance of the cure-rate in relation to the pathology is shown by Smith (1948) in his review of 242 nephrectomies done on patients with hypertension and various renal diseases, his cure-rate being only 19% However, his criteria for cure were rather rigid, and we prefer a higher residual systolic level than 140/90 mm Hg provided there is evidence of reversal of the disease in other organs, as was shown in the present case In the 21 selected cases with renal-artery stenosis the cure-rate for such severe hypertension is remarkable and shows that satisfactory treatment and recovery are possible when the present syndrome is correctly diagnosed

The varied effects of acute and chronic hypertension in the rat suggest the following alternatives

(1) If the hypertension is of short duration, either nephrectomy or removal of the constricted part of the renal artery should relieve the hypertension

(2) If the hypertension has lasted long enough, removal of the "clipped" kidney may be insufficient to relieve the hypertension, because the changes in the other kidney have become irreversible, and lumbodorsal sympathectomy also may be necessary

The challenge to the surgeon lies in a better preoperative selection of the patients who will benefit solely by nephrectomy The test of Howard et al (1954) is most important in this connection

Summary

A clinicopathological syndrome of hypertension which is cured by nephrectomy is discussed

Wilson and Byrom had previously described this syndrome in rats

A human case is now reported

A review of the published cases suggests that this syndrome is less rare than is usually supposed

Addendum

Since the preparation of this manuscript Poutasse and Dustan (1956) have described some cases of this syndrome

REFERENCES

Abeshouse, B S (1941) *Surgery*, 9, 942, 10, 147
Aronson, S M, Sampson, M C (1951) *Arch Path* 51, 30
Blacket, R B, Sellers, A L (1951) *Clin Sci* 10, 177
Blackman, S S, Jr (1939) *Bull Johns Hopk Hosp* 65, 353
Blahd, W H, Marcus, R, Wasserman, M R (1952) *Ann intern Med* 37, 179
Bourne, W A (1954) *Brit med J* ii, 271
Daniel, P M, Peabody, C N, Prichard, M M L (1952) *Quart J exp Physiol* 37, 11
— Prichard, M M L, Ward-McQuaid, J N (1954) *Brit J Surg* 42, 81
Fishberg, A M (1941) *J Amer med Ass* 119, 551
Freeman, N E, Leeds, F H, Elliott, W G, Roland, S I (1954) *ibid* 156, 1077
Goldblatt, H (1948) The Renal Origin of Hypertension Springfield, Ill
Goodman, H L (1952) *New Engl J Med* 246, 8
Hoffman, B J (1942) *J Amer med Ass* 120, 1028
Howard, J E, Berthrong, M, Gould, D M, Yendt, E R (1954) *Bull Johns Hopk Hosp* 94, 51
— Conner, T B, Thomas, W C, Jr (1956) *Trans Ass Amer Phycns* 69, 291
Hussar, A E, Bornstein, S (1954) *N Y St J Med* 54, 1670
Leiter, L (1938) *J Amer med Ass* 111, 507
Masuloff, S, Macht, M B (1951) *J Urol* 65, 371
Perera, G A, Haelig, A W (1952) *Circulation*, 6, 549
Perry, C B (1945) *Brit Heart J* 7, 139
Pickering, G W, Prinzmetal, M (1938) *Clin Sci* 3, 211
— Wright, A D, Heptinstall, R H (1952) *Lancet*, ii, 952
Poutasse, E F, Dustan, H (1956) *Cleveland Clin Quart* 23, 3
Prinzmetal, M, Hiatt, N, Tragerman, L J (1942) *J Amer med Ass* 118, 44
Smith, H W (1948) *Amer J Med* 4, 724
Stewart, C F (1941) *J Amer med Ass* 114, 2099
Thompson, J E, Smithwick, R H (1952) *Angiology*, 3, 493
Volhard, F, Fahr, T (1914) Die Brightsche Nierenkrankheit Berlin
Wainwright, J (1949) *Lancet*, i, 62
Wilson, C (1953) *ibid* ii, 579, 632
— Byrom, F B (1939) *ibid* i, 136
Yuile, C L (1944) *Amer J med Sci* 207, 394

NUCLEAR CHANGES IN ORAL EPITHELIAL CELLS IN SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD DUE TO VITAMIN-B_{12} DEFICIENCY

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To make the diagnosis of subacute combined degeneration of the spinal cord due to vitamin-B_{12} deficiency is seldom difficult when there is a concomitant megaloblastic anæmia with a histamine-refractory achlorhydria But when there are no changes in the blood and bone-marrow the clinical picture differs little from that of other diseases affecting the posterior and lateral columns Formerly the diagnosis could be reached only *ex juvantibus*, on improvement under treatment with liver extract or vitamin B_{12}, but in recent years more certainty has been obtained by demonstrating a low serum-vitamin-B_{12} level (Mollin and Ross 1954, Victor and Lear 1956, Killander 1958, Spray and Witts 1958) or an impaired

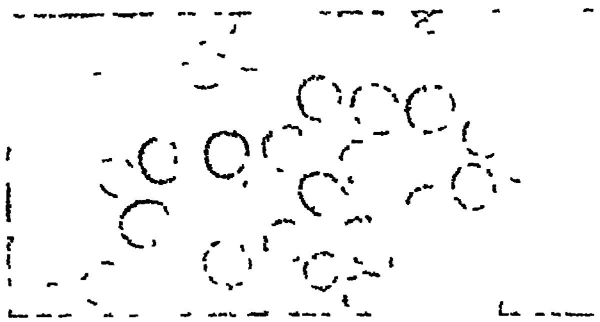

Fig 1—Blood-picture before treatment (×720.)

absorption test with radioactive vitamin B_{12} (Berlyne et al. 1957).

One of us described nuclear changes in oral epithelial cells in patients with pernicious anæmia (Boen 1957). In association with marked nuclear polymorphism, the presence of giant nuclei was characteristic. The nuclei were more or less round and had a finely reticulate chromatin structure. Their greatest diameter was on the average, above normal. Farrant (1958) found that both the longer and the shorter axes of the nuclei were higher in pernicious anæmia than in controls—especially the shorter. This last finding can, we think, be explained by so many of the nuclei being nearly round.

The question arose whether the nuclear changes would be found also in those rare cases in which vitamin-B_{12} deficiency is manifested by neurological disorders without hæmatological changes (Boen 1957). Recently we were able to study such a case.

Method of Investigation

The patient is asked to rinse his mouth thoroughly three times with physiological saline solution so as to remove food remnants. The mouth is then washed twice again, and the material thus obtained is centrifuged for about 10 minutes at 1000 r.p.m. The sediment is smeared evenly on microscope slides with a vaccinostyle, air-dried, and stained with May-Grünwald-Giemsa stain. A hundred consecutive nuclei are measured in their greatest diameter with an ocular micrometer using an oil-immersion objective.

Normally a maximum of 5% of the nuclei have diameters of 14·5 μ or more; in seven out of ten patients with pernicious anæmia the nuclei were definitely abnormal; in these seven cases we found the large nuclei in an average of 26%.

Case-report

Miss A, aged 57, had worked as a charwoman for the past six years without any long absences through illness. In July, 1957, she noticed tingling at the volar side of the fingers, but it did not interfere with her work. In October she complained of increasing general weakness, and had to take to her bed. She had uncontrolled jerks of the legs, paræsthesiæ, and numbness of the feet, and could barely walk from bed to table. In December she was admitted to the Burgerziekenhuis.

Examination showed no anæmia, icterus, or œdema; the liver and spleen were not enlarged. There was no glossitis, and the tongue was normally papillated except at the edges. Dr. S. Waterman, neurologist, found hypotonia and paresis in both legs (affecting the proximal part more than the distal), hyperactive patellar and Achilles reflexes, and slight ataxia. Somewhat later Dr. P. L. Braat, neurologist, also found impaired vibration sense in both legs and loss of position sense in the toes. There were bilateral extensor plantar responses, positive Chaddock and Mendel-Bechterew reflexes, and on the left side knee clonus. The cerebrospinal fluid was normal in pressure, clear, and colourless, and contained no granulocytes; the Wassermann, Pandy, and Nonne reactions were all negative.

Hæmoglobin 14 g. per 100 ml. Sedimentation-rate (Westergren) 7 mm. in one hour. Serum not icteric. Leucocytes 7800 per c.mm. (eosinophils 1%, granulocytes 69%, lymphocytes 24%, monocytes 6%). No hypersegmentation of granulocytes. Erythrocytes normal (except for slight anisocytosis); no megalocytes (fig. 1). Number of platelets normal. Bone-marrow picture entirely normal; no megaloblasts or giant metamyelocytes. Reticulocyte-count 1·5%. Serum-iron concentration 140 γ per 100 ml. (normal).

Fig 2—Mouth-washing before treatment. Giant nucleus beside normal ones. (×900.)

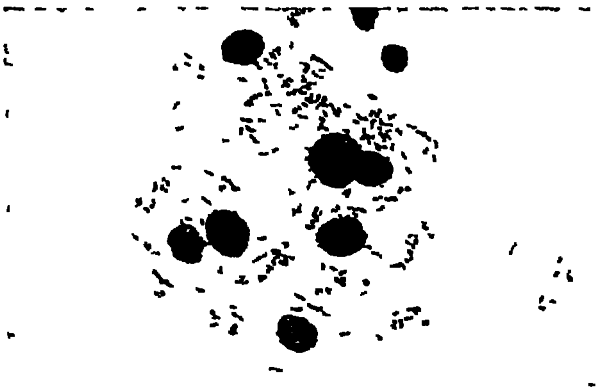

Fig 3—Mouth-washing before treatment. Polymorphism of nuclei. Typical of vitamin-B_{12} deficiency. (×400.)

Gastric analysis showed histamine-refractory achlorhydria. The luetic serological reactions were negative. The urine, with a specific gravity of 1·029, contained no urobilin.

In contrast to the hæmopoietic system the oral epithelial cells were distinctly abnormal. There was pronounced polymorphism of the nuclei and there were characteristic giant nuclei, more or less round and with a finely reticulate chromatin structure (fig. 2). 19% of the nuclei had a diameter of at least 14·5 μ, compared with 5% or less in normal people (fig. 3).

A diagnosis of vitamin-B_{12} deficiency was made on these changes in the epithelial cells of the mouth, and the patient was treated with 100 γ vitamin B_{12} by intramuscular injection daily for 3 weeks, and thereafter once a week. Her legs gradually grew stronger and after a month she could walk short distances without support. The paræsthesiæ, the numbness, and the abnormal reflexes disappeared. The slight ataxia and the impairment of vibration sense remained.

The administration of vitamin B_{12} had no influence on the reticulocyte-counts, the hæmoglobin concentration, or the serum-iron level. These prove that the hæmopoietic system had not suffered from the deficiency.

The oral epithelial cells were normal again a week after the beginning of treatment. Fig. 4 shows the distribution of the nuclei on different days: by the 5th day large nuclei had disappeared. This reaction to vitamin B_{12} is similar to that of patients with classical pernicious anæmia (Boen 1957). In fig. 5 the more monomorphic picture of the nuclei can be seen.

Another proof of the correctness of the diagnosis was the low serum-vitamin-B_{12} level before treatment—namely, 60 μμg

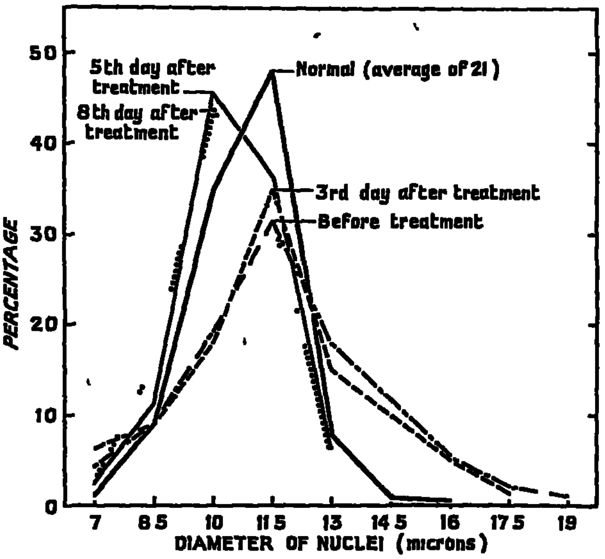

Fig 4—Distribution of nuclei on different days after beginning treatment with vitamin B_{12}

per ml (normal 150–500 μμg) * The outcome was known to us only later, when the patient was recovering

Discussion

It is generally agreed that patients with subacute combined degeneration of the spinal cord concomitant with pernicious anæmia have a low serum-vitamin-B_{12} level, whereas in those with other neurological disorders it is normal (Mollin and Ross 1954, Victor and Lear 1956, Killander 1958, Spray and Witts 1958) The absorption test with radioactive vitamin B_{12} has also been used for the differential diagnosis of neurological diseases (Berlyne et al 1957) This test is not always useful, because impaired absorption is not necessarily associated with deficiency, since there may be a large stock of vitamin B_{12} in the body Again, though absorption is normal, there may be deficiency because the diet, over a long period, contains too little vitamin B_{12}, as in some vegetarians (Badenoch 1956, Booth and Mollin 1957) The characteristic changes in the nuclei of the oral epithelium, however, appear to be definite evidence of vitamin-B_{12} deficiency Their detection is easy and the method is suitable for clinical purposes

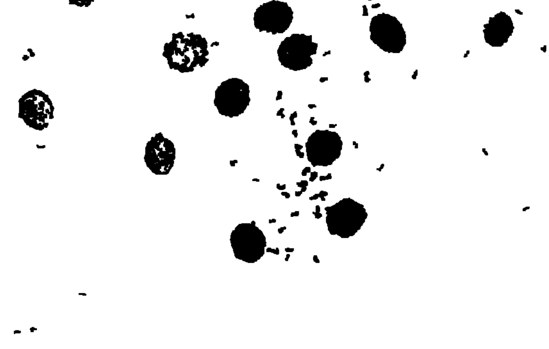

Fig 5—Mouth-washing on 8th day of treatment Normal picture (×400)

A normal nuclear pattern does not exclude a vitamin-B_{12} deficiency In three out of ten patients with perniciou anæmia the nuclei were normal (Boen 1957) Farran (1958) also found a normal average diameter in some o his patients

Summary

A woman, aged 57, had had subacute combine degeneration of the spinal cord for several months, bu showed no changes in the blood or bone-marrow Th diagnosis of vitamin-B_{12} deficiency was made on charac teristic nuclear changes in the oral epithelium On treat ment with vitamin B_{12} she much improved and th nuclei of the oral epithelium became normal within week of the start of treatment No changes were seen i the hæmoglobin concentration, reticulocyte-counts, o serum-iron level The diagnosis was confirmed b demonstration of a low serum-vitamin-B_{12} level befor treatment (60 μμg per ml)

We are grateful to Prof J G G Borst for his encouragement, to Mrs J M den Ottolander-Claremont for correcting our English and to Organon-Oss for estimating the serum-vitamin-B_{12} level

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* The assay was done in the microbiological department of Organon-Oss, using *Lactobacillus leichmannii*

REFERENCES

Badenoch, J (1956) *Proc R Soc Med* 47, 426
Berlyne, G M, Liversedge, L A, Emery, E W (1957) *Lancet*, i, 294
Boen, S T (1957) *Acta med scand* 159, 425
Booth, C C, Mollin, D L (1957) *Lancet*, i, 375
Farrant, P C (1958) *ibid* i, 830
Killander, A (1958) *Acta med scand* 160, 75
Mollin, D L, Ross, G I M (1954) *Proc R Soc Med* 47, 428
Spray, G H, Witts, L J (1958) *Brit med J* i, 295
Victor, M, Lear, A A (1956) *Amer J Med* 20, 896

SARCOIDOSIS OF LIVER AND SPLEEN

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Sarcoidosis is now being diagnosed more often than formerly Its ætiology is still a subject of controversy Whereas many physicians regard sarcoidosis as an unusual response to tuberculous infection, others regard it as a reaction to various exciting causes

Sarcoidosis may affect the skin lymph-nodes, the eyes, the salivary glands, the lungs, the bones of the hands and feet, the liver, and the spleen The Mantoux reaction is often negative but may be positive, and then usually only weakly so The lesions are granulomatous and resemble tubercles, but caseation is absent, and tubercle bacilli are never found

The case reported here is unusual for three reasons the sarcoid lesions were demonstrable only in the liver and spleen, the patient was aged only 13, and the spleen ruptured, enabling us to follow the effect of splenectomy on the disease

Case-report

A boy, aged 13, attended Harefield Hospital on July 29, 1956, with two months' history of being off colour, with periodic attacks of epigastric pain and vomiting associated with rigors and anorexia He had possibly been jaundiced a month before Recently he had had pain in the left lower part of his chest, with a feeling of tightness on breathing and coughing There was nothing relevant in his past or his family history

Nine siblings had been free from similar illness

On admission to hospital on July 29, 1956, the patient looked pale and ill but was not jaundiced His temperature was 99°F and pulse-rate 76 The only abnormal physical signs were some impairment of percussion note, weak breath sounds at the left base, and a liver that was just palpable

Investigations—Radiography of his chest showed opacity at the left base but no abnormal hilar shadows Bronchography showed a normal bronchial tree The Mantoux reaction was positive at 1/100, but the reaction was not brisk Acid-fast bacilli were not seen or cultured in thirteen specimens of sputum The urine contained no bile or urobilinogen The erythrocyte-sedimentation rate (E S R.) was 20 mm at the end of one hour (Westergren), and the white blood-cells numbered 7500 per c mm

Progress—For two weeks the patient's evening temperature was 99°F (see figure) The E S R was 8 mm at the end of one hour at the end of this time 'Distaquain' penicillin 300,000 units was then given for eight days, during which time his evening temperature fell to 98 4°F, but it rose to 99 8°F when the penicillin was withheld and fell to 98·4°F when the penicillin was resumed Then the boy was allowed home for a weekend On his return he said that on the previous evening he had had abdominal pain and a headache and had vomited He felt better on return but looked ill and tired, and his temperature had risen to 100°F Jaundice was absent, and no lymph-nodes were palpable. His spleen had become palpable and his liver larger The Paul-Bunnell reaction was negative, a blood-culture was sterile, the Wassermann reaction and the Kahn test were negative, and acid-fast bacilli were not found either on direct examination or on culture on numerous occasions throughout his illness Reticulocytes were less than 1%, and sternal marrow showed a maturation defect of red and white series Liver-function tests showed alkaline phosphatase 8 King-Armstrong units, bilirubin 0 2 mg per 100 ml, thymol turbidity 1 unit, no flocculation, total protein 7 12 g per 100 ml (albumin 5 25 g per 100 ml., and globulin 1 87 g per 100 ml) The liver and spleen continued to increase in size, and the temperature swung between 100° and 104°F Penicillin appeared to lower the temperature to 99°F in the evenings There was still no other abnormality, so on Sept. 14, 1956, the abdomen was opened

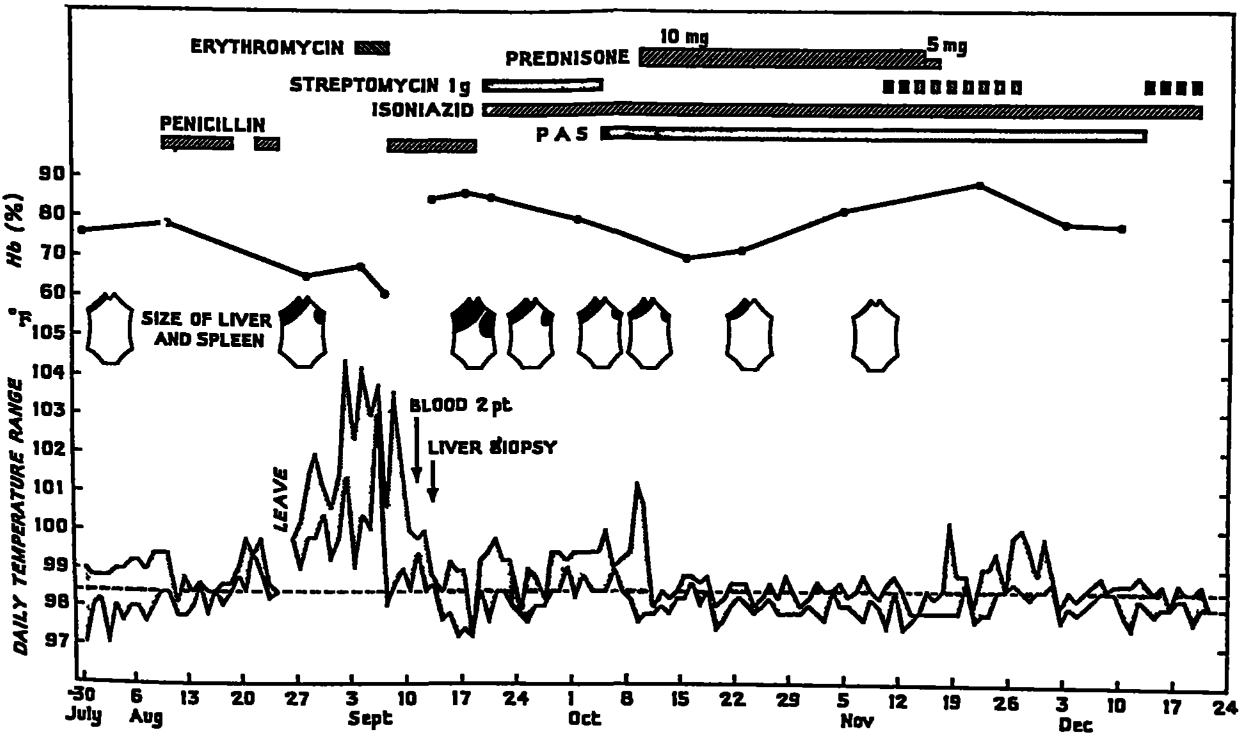
On laparotomy the liver was found to be enlarged and looked normal but was rather firm The spleen was smooth and much enlarged No other abnormality was found in the abdomen A biopsy specimen taken from the liver showed scattered aggregations of epithelioid cells, some with giant cells, there was no caseation, and tubercle bacilli were not seen Sarcoidosis was diagnosed

Postoperative course—This was uneventful, and treatment with isoniazid and streptomycin was started Because of hypersensitivity p- aminosalicylic acid was later substituted for the streptomycin The liver became a little smaller, but the boy was still pyrexial and miserable Treatment with prednisone produced a dramatic response the boy looked better, his pyrexia fell by crisis, and in forty-eight hours his liver was much smaller and his spleen impalpable His liver continued to decrease, and the drugs were stopped He had slight pyrexia for a fortnight after the prednisone had been stopped, but thereafter his temperature was normal

On discharge in March, 1957, he was apyrexial and had put on weight, and neither liver nor spleen were palpable The E S R was 20 mm at the end of one hour (Westergren) During all this time he had remained anæmic At the onset his hæmoglobin was 68%, white-cells 3500 per c mm, and platelets 100,000 per c.mm This condition was unaffected by chemotherapy and parenteral iron Prednisone, however, caused the hæmoglobin to increase by 20%

Readmission—In August, 1957, because of pyrexia and occasional nausea and vomiting the patient was reinvestigated During ten days in hospital he had no pyrexia and no abnormal physical signs Liver-function tests were normal, agglutination reactions against salmonella and brucella were negative, the hæmoglobin was 80%, and the E S R was 20 mm at the end of one hour (Westergren)

Rupture of spleen—On Sept 6, 1957, the boy was thrown off his bicycle, striking his left side on the handlebars He was admitted to Mount Vernon Hospital half an hour later He complained of severe upper abdominal pain, mainly on the left side



Treatment and progress

On examination he was vomiting and presented the signs of acute hæmorrhage, his abdomen was tender all over but maximally in the left hypochondrium, where guarding was present His abdomen was slightly distended, and shifting dullness was present on the right side Shoulder pain was absent

At laparotomy by Mr Alan Shorter two hours later, his abdomen was found to contain a pint and a half of blood, and there was a tear at the hilum of the enlarged spleen Splenectomy was done and three pints of blood transfused Convalescence was uneventful, and the boy was discharged on the eleventh postoperative day with hæmoglobin 74%

Operation specimen —The excised spleen weighed 370 g (normal for age, 100 g) and had a transverse tear extending from the hilum for 5 cm Its capsule was smooth and covered with blood-clot On section a central band of hæmorrhage at the site of the tear was seen, flanked by pale splenic substance showing fine white mottling Microscopy showed an area of interstitial hæmorrhage surrounding the tear and the typical appearances of active sarcoidosis in the splenic substance (small aggregations of epithelioid cells, some with giant cells, surrounded by a thin zone of lymphocytes, but no caseation)

Follow-up —Seen on Dec 13, 1957, three months after the operation, the boy was in excellent clinical condition His liver was impalpable, his hæmoglobin 92%, E S R 8 mm at the end of one hour (Westergren), white cells 12,100 per c mm (polymorphs 45%, lymphocytes 46%, eosinophils 6%, basophils 2%, monocytes 1%)

Comments

In this case the presenting symptoms of pyrexia and malaise were probably due to the sarcoid lesion The cough and tight feeling in the left side of the chest may have been due to the slight changes in the left base but were more probably due to irritation of the diaphragm by an enlarging spleen

Antituberculous drugs were without much effect, but prednisone appeared to suppress the disease That it was only suppression was realised ten months later, when section of the spleen showed active sarcoid The figure shows the increase of hæmoglobin associated with prednisone therapy and the relapse following its withdrawal The recurrence of anæmia suggests that the course of prednisone was inadequate Since the depressed hæmopoiesis caused few symptoms, surgery was not considered, but it became compulsory later by rupture of the spleen and then produced an increase of hæmoglobin, a rise in the white-cell count, and much improvement in the patient's general condition

We have watched this case for eighteen months and have at no time found any evidence of sarcoid lesions elsewhere The initial lesion in the chest did not resemble pulmonary sarcoid This is very unusual, and we have only been able to find one definite case with similar features published (Kay 1950)

Discussion

Sarcoidosis may be generalised or may appear in well-recognised groups of tissue

Mather et al (1955) have shown that, in all types of sarcoidosis, liver biopsy is positive in 63% of patients and the spleen is palpable in 14% Necropsy results put the incidence of splenic involvement at 50% (Branson and Park 1954), this is likely to be due to the impossibility of detecting slight enlargement of the spleen clinically and to the infrequency of splenic biopsy In this country involvement of the liver and spleen is generally silent and the patient is only conscious of the disease elsewhere In America cases of gross involvement of the liver and spleen, with symptoms of liver failure, have been described, but most of these are associated with manifestations elsewhere

Liver in Sarcoidosis

Although the liver is so often involved and enlarged in sarcoidosis, evidence of disordered function is uncommon in this country In the series of Mather et al. (1955) only 10% of the cases showed a raised serum-globulin level, and the finding bore no relationship to the presence or the absence of sarcoid lesions in the liver In the present case liver function was normal throughout

Jaundice is rare, Branson and Park (1954) found only 3 certain cases in 867 cases of sarcoidosis

Liver failure can occur in sarcoidosis, Branson and Park (1954) describe a fatal case in which jaundice, ascites, and hæmorrhage occurred

Kelley and McHardy (1955) report a man, aged 48, who developed obstructive jaundice due to hepatic sarcoid lesions The liver became fibrotic, and he died in liver failure He was treated with corticotrophin and deep X rays, the latter may have been a major factor in producing the cirrhosis

In these cases hepatic involvement was only part of a generalised sarcoidosis

Spleen in Sarcoidosis

Involvement of the spleen in the present case produced hypersplenic anæmia and was a contributory factor in rupture of the spleen

Hæmopoietic dysfunction is not uncommon in sarcoidosis Hypersplenism may depress the red cells, white cells, or platelets, either severally or together In the present case the red-cell count was chiefly affected, and the white-cell count during hyperpyrexia fell to 3500 per c mm , and for three months (from September to November, 1956) the platelet-count was 100,000–150,000 per c mm There were no purpuric manifestations Bruschi and Howe (1950) described a case in which splenectomy had to be done to relieve purpura

It is thought that the anæmia is due to exaggeration of the normal inhibition of the bone-marrow by the spleen Whether prednisone increased the hæmoglobin by acting directly on the marrow or by decreasing the volume of the spleen and the sarcoid lesions contained therein is questionable Shulman et al (1952) noted, in a series of cases, that corticotrophin caused rapid regression of hepato-splenomegaly, with occasional improvement of anæmia, but in most cases relapse followed the withdrawal of corticotrophin The similar effect produced by splenectomy has been recorded by Longcope and Freiman (1952) and Kay (1950)

Nausea, vomiting, and pain in the chest were all probably related to splenomegaly Splenectomy was done by Partenheimer and Meredith (1950) to relieve these symptoms

Spontaneous rupture of the spleen from sarcoidosis was the presenting symptom in a case described by James and Wilson (1946) and another by Phillips and Luchette (1952) The former patient was a man, aged 49, who had pulmonary lymphadenopathy and a normal-sized spleen, the diagnosis was made on finding sarcoid lesions in the spleen The latter patient was a man, aged 21, who had lymphadenopathy and a spleen weighing 306 g Neither of these patients had isolated sarcoidosis of liver or of spleen In the present case the rupture was traumatic, but probably the trauma would not have ruptured a normal spleen This accident enabled us to observe the persistence of the sarcoid lesions despite antituberculous chemotherapy and a short course of prednisone It also suggests that splenectomy would have controlled the anæmia had it been done before the rupture

Summary

A case of sarcoidosis of the liver and spleen is described in a boy, aged 13, complicated by hypersplenism and traumatic rupture of the spleen

We wish to thank Dr E Idris Jones, consultant physician, who originally referred the patient, Mr David Levi, consultant surgeon, for the liver biopsy, Dr E Nassau, pathologist and his staff for the histology of the liver biopsy, and Dr G S W Andrews and Dr J M Bennett, pathologists, of Mount Vernon Hospital, for the report on the spleen, and Mr A Shorter, consultant surgeon, for the splenectomy

REFERENCES

Branson, J H, Park, J H. (1954) *Ann intern Med* 40, 111
Bruschi, M, Howe, J S (1950) *Blood*, 5, 478
James, I, Wilson, A J (1946) *Brit J Surg* 33, 280
Kay, S (1950) *Amer J Path* 26, 427
Kelley, M L, Jr, McHardy, R. J (1955) *Amer J Med* 18, 842
Longcope, W T, Freiman, D G, (1952) *Medicine, Baltimore*, 31, 1
Mather, G, Dawson, J Hoyle, C (1955) *Quart J Med* 24, 331
Partenheimer, R. C., Meredith, H C, Jr (1950) *New Engl J Med* 243, 810
Phillips, A K., Luchette, A. A (1952) *Ohio St med J* 48, 617
Shulman, L. E, Schoenrich, E H., Harvey, A M (1952) *Bull Johns Hopk Hosp* 91, 371

DISSEMINATION OF MICRO-ORGANISMS BY A SURGICAL PUMP

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IN a case of staphylococcal subphrenic abscess treated by suction drainage by an electric pump it was noted that the outlet from the pump discharged directly into the ward When the air from the outlet of the pump was led to a slit sampler, it was found that large numbers of organisms were being ejected by this route

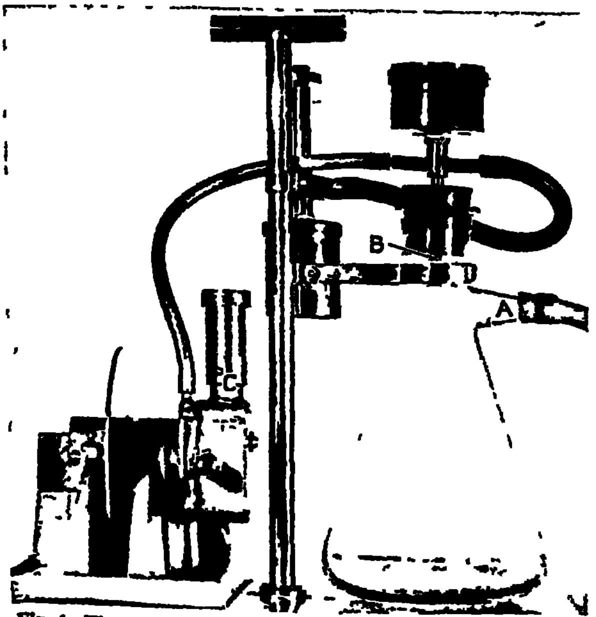


Fig 1—The pump assembly A, input to trap, B, outlet from trap to pump; C, outlet from pump (as modified)

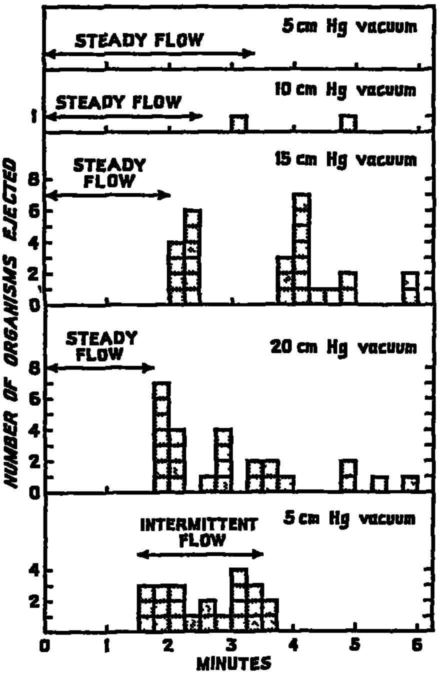


Fig 2—Numbers of organisms ejected from pump outlet at different pressures and flows

Since the discharge of organisms in this way into a surgical ward was clearly undesirable, experiments were instituted to show the degree of contamination of the atmosphere in this way and to find a way to prevent it

Degree of Contamination

The input to the trap (fig 1, A) was immersed in 200 ml of broth culture containing 100,000,000 organisms per ml, and the outlet from the pump (fig 1, C) was led by a sterile plastic tube to a slit sampler The pump was run at negative pressures of 5, 10, 15 and 20 cm Hg

Fig 2 shows representative examples of the results obtained With a vacuum of 5 cm Hg no organisms were ejected With the greater negative pressures used no organisms were ejected during the flow of the liquid, but a shower of organisms was ejected when the container emptied and air and froth were drawn rapidly into the trap (fig 2) The number of organisms ejected increased with increase of the vacuum, and this was partly because bubbles in the trap came into direct contact with the tube (fig 1, B) leading to the pump

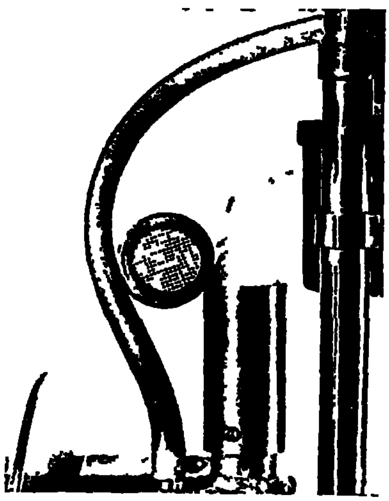


Fig 3—Filter assembly showing brass cylinder, mesh cap, and cotton-wool

In view of the importance of splashing and the likelihood of this occurring in practice when the drained cavity empties, experiments were conducted in which the

200 ml of culture was delivered at intervals by a siphon in 20-ml amounts In this way repeated splashing and frothing occurred In these circumstances 5–10 times as many organisms were ejected as when the same volume was delivered by direct flow (fig 2)

Prevention

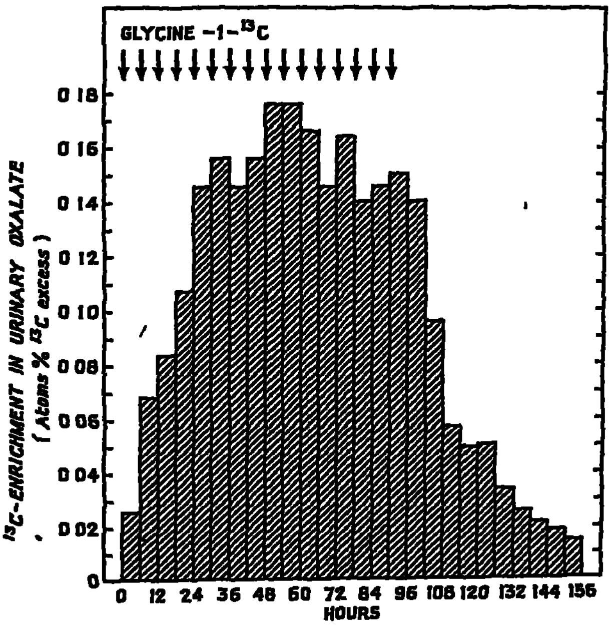
Ejection of organisms from this system was completely abolished by fitting to the output of the pump a brass sleeve, with a mesh floor and cap, lightly packed with non-absorbent cotton-wool (fig 3) This filter has remained effective during 24-hour periods of continuous running of a modified experimental system in which 20 ml amounts of culture were delivered at intervals of 2 minutes In practice the non-absorbent cotton-wool has been replaced every 24 hours when the pump was in continuous use

The brass sleeve was made by Mr D Brown, of the electrical engineer's department, Middlesex Hospital, and costs about 7*s* 6*d*

Preliminary Communications

INCORPORATION OF CARBOXYL-CARBON ATOM OF GLYCINE INTO OXALATE IN A CASE OF PRIMARY HYPEROXALURIA

PRIMARY hyperoxaluria [1] is characterised biochemically by a continuous urinary oxalate excretion equivalent to about 100–200 mg $(COOH)_2$ $2H_2O$ per 24 hours (The corresponding figure for normal people is less than about 40 mg) Clinically, these patients present in childhood with recurrent multiple calcium-oxalate urinary calculi and nephrocalcinosis, they die prematurely from renal failure, and at necropsy calcium oxalate crystals are demonstrable in some of the extrarenal tissues [2] Previous studies in this laboratory suggested that glycine is the precursor of at least some of the oxalate which they excrete [3]



The ^{13}C abundance in the calcium oxalate isolated from successive 6-hour urine collections in a case of primary hyperoxaluria given glycine-1-^{13}C orally at the times indicated by arrows

We recently administered glycine-1-^{13}C orally (2 56 mg per kg body-weight, 49 8 atoms % ^{13}C excess, 6-hourly for 4 days) to a patient with primary hyperoxaluria, the oxalate was isolated from successive 6-hour urine collections and its ^{13}C content measured There was prompt and considerable incorporation of the isotope into the urinary oxalate (see figure) This relation between glycine and oxalate in primary hyperoxaluria accords with our previous observation that in this disease large doses of sodium benzoate (given to deplete the free-glycine metabolic pool) decrease the urinary excretion of oxalate [3]

It has been shown that enzyme systems capable of degrading glycine via glyoxylate to formate and carbon dioxide are present in some mammalian tissues [4], also (during in-vitro experiments with rat liver) that, if the degradation of glyoxylate to formate and carbon dioxide becomes the rate-limiting step in the reaction sequence, oxalate is synthesised [5] Although our present findings are compatible with the view that the metabolic lesion of primary hyperoxaluria is in this path of glycine metabolism, they do not show whether the primary abnormality is (a) a failure to degrade glyoxylate to formate and carbon dioxide, or (b) an excessive—possibly abnormal—conversion of glycine to glyoxylate, the further metabolism of which is inherently limited

Other cases of primary hyperoxaluria are being studied, and we are comparing the isotope enrichment in the free urinary glycine (which we regard as a valid sample of the free-glycine metabolic pool [6]) with the isotope enrichment in the urinary oxalate The results of these investigations will be reported in detail elsewhere

We are indebted to Prof A Wormall, F R S , for facilities for the mass spectrometric analyses, and to our assistants Miss E D Bell and Mr L Rawlings for their help

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[1] Archer, H E , Dormer, A E , Scowen, E F , Watts, R W E *Lancet*, 1957, ii, 320

[2] Scowen, E F , Stansfeld, A G , Watts, R W E *J Path Bact* (in the press)

[3] Archer H E , Dormer, A E , Scowen, E F , Watts, R W E *Brit med J* 1958 i, 175

[4] Weinhouse, S Symposium on Amino-acid Metabolism (edited by W D McElroy and H B Glass) p 637 Baltimore, 1955

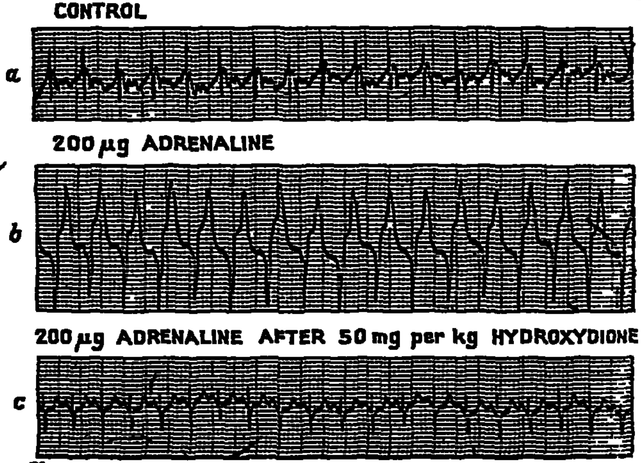
[5] Nakada, H I , Friedmann, B , Weinhouse, S *J biol Chem* 1955, 216, 583

[6] Crawhall, J C , Watts, R W E *Biochem J* 1958, 69, 22 P

INHIBITION BY HYDROXYDIONE OF ADRENALINE-INDUCED ARRHYTHMIAS

DURING animal experiments, one of us (N R W T) noted that hydroxydione (21-hydroxypregnane-3, 20-dione sodium succinate) appeared to arrest cardiac arrhythmias in the isolated rabbit heart and to prevent their occurrence in cats A preliminary series of experiments has now been done to see if this drug would prevent arrhythmias induced with adrenaline

Five healthy cats were used, varying in weight from 2 to 3 5 kg They were lightly anæsthetised with ether, a tracheal cannula was inserted, and the blood-pressure was recorded from the carotid artery with a mercury manometer The drugs were given intravenously into the femoral vein The vagi were left intact, and continuous electrocardiograms were recorded using lead aVF as a control Gradually increasing doses of adrenaline, within the range 100–500 µg , were given intravenously and a



Showing the production of ventricular tachycardia in (*b*) and its prevention by hydroxydione in (*c*)

great variety of arrhythmias were induced—ectopic beats from multiple foci, coupled rhythm, nodal rhythm, and paroxysmal tachycardias The dose, which varied greatly from cat to cat, was stepped up in each case until paroxysmal ventricular tachycardia could be consistently produced 50 mg of hydroxydione per kg body-weight was then given intravenously, and after 6 minutes the previously determined dose of adrenaline was repeated In four out of five cats none of the previously recorded arrhythmias occurred (see figure), and after 50 to 100 mg hydroxydione per kg body-weight the dose of adrenaline had to be increased by 50–300% before the tachycardia was reproduced

It may be that hydroxydione or one of its congeners could prevent arrhythmias induced in other ways, and might be useful as an anæsthetic agent during cardiac surgery These possibilities are under study

We are indebted to Messrs Organon Laboratories for a supply of hydroxydione

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Reviews of Books

Clinical Electrocardiography

The Spatial Vector Approach ROBERT P GRANT, M D, National Heart Institute, National Institutes of Health, Bethesda, Maryland London and New York McGraw-Hill 1958 Pp [illegible] 58s 6d

THIS outstanding book on clinical electrocardiography is based on a study of the direction of spread of the electrical forces of the heart as shown by the spatial vector It is Dr Grant's opinion that no loops need be actually calculated and no special apparatus is required He emphasises that the direction of the loop can be appreciated with sufficient accuracy by simply studying the standard limb and chest leads of the electrocardiogram.

The electrocardiogram is a graphic record of the electrical impulses which spread from the sino-atrial node across the atria to the atrioventricular node and then via the bundle of His to the ventricles These electrical forces are transmitted to the surface of the body and may be tapped at different points by leads attached to the limbs or chest wall—the electrocardiogram The form of the electrocardiogram in any one lead was once thought to reflect action potentials underlying the electrode, but it is now appreciated that it is merely tapping at one point the circuit of electrical forces which is described as the spatial vector or loop Thus, the electrocardiogram represents the total electric forces at the point on the limbs or chest wall from which the lead is taken, and is as much influenced by abnormalities of ventricular muscle on the opposite side of the heart as it is by abnormalities beneath the electrode The negative wave or Q wave of anterior chest leads in anterior cardiac infarctions, therefore, merely represents a retreat of the electrical forces posteriorly, away from the damaged area, and is accompanied by an increase in height of the R wave in posterior leads Conversely, in posterior cardiac infarction an increase in height of the R in anterior chest leads is just as important as the presence of a Q wave posteriorly

This is the vectorial approach and Dr Grant uses it to explain the whole of electrocardiography If this concept can be understood the laborious memorisation of electrocardiographic patterns becomes unnecessary Dr Grant's book should be read and re-read by every cardiologist or anyone training in cardiology The reader is not presented with a series of loops divorced from electrocardiograms, but is shown how to deduce the pattern of this loop from the routine electrocardiogram Knowledge of the approximate pattern of the loops greatly helps in basic interpretation, but the finer points for diagnosis are still obtained from changes in the form of the QRST complex picked up in individual leads The vector approach however, gives a broad view of the whole picture and is valuable for *understanding* abnormalities shown in the electrocardiogram

Although this is a book of first principles it is not a suitable book for the beginner, or for the occasional electrocardiographer, who will have to await a simpler volume, but preferably one based on the same principles

Law and Ethics for Doctors

STEPHEN J HADFIELD, M.B, D OBST, assistant secretary, British Medical Association London Eyre & Spottiswoode 1958 Pp 388 42s

IN the hundred years since the first Medical Act of 1858, few of the changes in the practice of medicine have made its conduct simpler, for increasing specialisation, the influence of the State, and the criticism of a more educated public have brought appreciable complications During the century, however, the profession has tested the principles of conduct which were its inheritance, and proved their fundamental strength These have remained constant while practice has altered, keeping in step with the community's needs

In this book Dr Hadfield has described the many points at which medicine makes contact with the community With so much ground to cover, some lack of detail or significant omissions might be pardoned, in fact, the book is outstandingly comprehensive, and even where complicated legal principles are being explained, the information is clearly presented Whether describing the ethical position of a doctor who broadcasts, the legal procedure of the Coroner's Court, or prescribing in the National Health Service, Dr Hadfield is readable and interesting

It is possible to practise for years, maybe a lifetime, without direct knowledge of the workings of courts of law, and of the many committees and tribunals which now exist under the National Health Service Many doctors have a vague impression of their existence and function somewhere in the professional background This book will give them a clearer picture To some extent it is also a catalogue of present-day medical thought and custom, and as such it is a historical document Moreover it is a source-book for the teacher of the undergraduate and the new entrant to practice, and a work of reference for the established practitioner

Does the place of the doctor in relation to the community, as here described, receive sufficient attention in the formal teaching of the medical student? There is much to be said for encouraging the student to make himself more fully aware of his future responsibilities towards his patients, his profession—and himself

Modern Trends in Endocrinology

Editor H Gardiner-Hill, M D, F R C P, consulting physician, St Thomas's Hospital, London London Butterworth 1958 pp 311 65*s*

This important Modern Trends series enables the clinician or the investigator to keep an eye on the growing points of knowledge that fall outside his own immediate interests Some sixteen subjects have now been covered, some of them by two or even three volumes, and this one is a notable addition It comprises 21 articles, about half of them devoted to the thyroid or the adrenal cortex The range is wide, and includes hormones of the adrenal medulla, serotonin, and gynæcological endocrinology The authors include physiologists, clinical investigators, and clinicians, and there is a pleasing variety about the style and approach of the different essays

Everyone, whether primarily an investigator or a clinician, will find something to his taste, and the postgraduate student will probably want to read the whole book But some readers will regret that in a book designed not only to satisfy curiosity but also to awaken interest the bibliographies do not include the titles of articles cited It is admittedly hard to persuade some authors to provide them, but the practice encourages the novice to explore his medical library, and saves the investigator some unnecessary excursions into it

Bridging the Gap

Editor R F Tredgold, M D, D P M, physician-in-charge, department of psychological medicine, University College Hospital, London London Christopher Johnson 1958 Pp 270 30*s*

Morbid public fascination by mental illness is well enough known and its dynamic origins are easy to understand not for nothing are new psychiatric works obligatory reading for Hollywood producers All too often what is written for the public is sensational, with grotesque distortions or malicious half-truths, and a book, therefore, which turns its back on Ruthless Exposures, and seeks rather to conciliate and explain, is to be welcomed Here a group of experts have written for the inquiring layman upon some aspects of the mental health services, and their sober reflections are placed alongside bitter and trenchant criticisms from ex-patients and others Emphasis is rightly placed on the harm done by mutual slanging matches between extremes of either side, and the need to travel the much harder road of reconstruction and improvement But this book is no act of whitewash Dr Donald Johnson, M P, hits out in one chapter with his customary vigour, and Dr J A R Bickford makes a splendid contribution on the psychiatrist's shortcomings and opportunities (his views should be obligatory reading for those in mental-hospital practice) Dr J A Scott has several chapters on the part played by the local authority, and, among others, Dr Desmond O'Neill writes on domiciliaries, Dr E W Dunkley on the observation ward, and Dr David Stafford-Clark on the psychopath There is an excellent brief account of the mental defective and a useful appendix summarising the laws related to mental hospital admission

It is perhaps inevitable that sensible balanced views should be slightly dull, but even allowing for this the book may disappoint some readers, perhaps because of the lack of continuity and repetitiveness But we hope it will reach the very wide public which it undoubtedly deserves

Marriage Counselling

J H Wallis, training officer, National Marriage Guidance Council, H S Booker, senior lecturer in statistics, London University London Routledge & Kegan Paul 1958 Pp 313 25*s*

This is an account by Mr Wallis of the origin, development, principles, and aims of the Marriage Guidance Council, the kind of problems brought by spouses in trouble, the methods of choosing and training counsellors (in detail) and (in less detail) the way they set about their work, followed by a statistical analysis by Mr Booker of some 25,000 "cases" recorded by counsellors in the years 1952–54, directed mainly to ætiology

Probably all family doctors over 40 and many other kinds of medical men or women have found themselves either essaying or resolutely declining the task of "marriage counselling" Of those not declining, probably only the few with psychiatric leanings and training—perhaps not even all these—will approach it without reluctance and misgiving It is surprising, then, that there is apparently no lack of volunteers ready to face a residential selection conference, based on the procedure of the War Office Selection Board, for the privilege of listening to and trying to help marriage partners in distress as "counsellors", part-time and unpaid No very clear picture emerges of the typical counsellor—if such a thing exists—either before or after training, and we do not know, for instance, whether a troubled spouse may expect to meet a counsellor of similar or dissimilar social or cultural class The chapters on the nature of counselling and people in difficulties are modestly and pleasantly written, but their matter is sadly familiar to the medical man and the results of statistical analysis seem also to confirm everyday experience Causes of trouble are multiple and complex—personality counts for more than environment, sexual difficulties are less intractable than those of character—and the broad results of "counselling" (a third helped, a third not helped, a third "result unknown") seem to justify the practitioner's misgiving when the history and symptoms of a sick marriage are laid before him

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Cunningham's Manual of Practical Anatomy (12th ed Vol III, Head and Neck Brain London Oxford University Press 1958 Pp 520 28*s*)—The main changes in this new edition, revised by the late Prof J C Brash, concern nomenclature and illustrations Many, but not all, of the alterations approved at the International Congress of Anatomy in Paris in 1955 have been accepted in this text Alternative terms are clearly indicated Twenty-one drawings have been replaced, and so have many radiographic plates This familiar manual may be judged lengthy by present-day standards, but it is still, we think, the best available dissection manual Since so many students today pay little heed to large systematic textbooks, even if they own them, it is all the more desirable that they should use an adequate practical manual Though the practice of relying wholly or largely upon a dissection handbook is to be deplored, Cunningham's manual is perhaps the best of guide-books to the human body The new edition is bound in washable material, and preserves its customary handsome appearance

Cardiovascular Collapse in the Operating Room (London Pitman Medical Publishing Co 1958 Pp 197 45*s*)—Death comes most dramatically in the operating-theatre, partly because of its unexpectedness It is on this point that the authors of this book, Dr Herbert Natof and Prof Max Sadove, of the University of Illinois College of Medicine, have much to say, for the gist of their message is that such deaths are usually associated with demonstrable disease which should have been detected clinically and suitable precautions taken Each predisposing cause is carefully considered in a book which will interest surgeons as much as anæsthetists

Smoking, Lung Cancer and You (London Lindon Press 1958 P 72 5*s*)—This short, easily read book by Dr Robert N C McCurdy presents for the lay reader the main facts concerning the dangers of tobacco-smoking It is well and interestingly written from a strongly individual viewpoint by a medical officer of health who, after studying the problem of lung cancer both nationally and in his own area, feels that the time has come for Government action The argument is well documented and doctors as well as laymen should find it helpful in assessing the social and political as well as the statistical aspects of this pressing present-day problem

THE LANCET

LONDON 9 AUGUST 1958

Heart-lung Machines

SINCE the methods of extracorporeal circulation were first put to clinical use, many rival schools of technique have evolved, each with its ardent supporters. In the early days there was little to choose between them: each had its list of surviving patients, and the causes of mortality were often ill understood; each had its technique to perfect before machines could be accurately compared. There are two fundamental methods of oxygenating blood—by bubbling oxygen through it[1] and by exposing a film of it to oxygen. The film method is subdivided into systems which use rotating discs[2-4] and those incorporating the stationary vertical screen.[5] Though figures have been compiled at each of the big centres using these different methods, a straight comparison between them is difficult for several reasons: the cases may be selected differently, the technical accomplishment of surgeons varies, and their presentation of results is often hard to assess. There is also a hidden factor which bears directly on the success of the operation: the length of time required to close an intracardiac defect must always depend on the dexterity of the surgeon, but the ultimate security of the closure—i.e., freedom from recurrence—may well depend on taking a rather longer time than is commonly required for the intracardiac operation. It has been clearly shown by VARCO et al.[6] that the duration of perfusion at lower rates of flow directly affects the survival-rates of patients. At rates of flow between 56 and 65 ml. per kg. per min. the duration of perfusion was less important, although none of the perfusions lasted longer than an hour. These results with a bubble oxygenator may discourage surgeons from using this type of apparatus, especially in adults. Safety is clearly the first and vital need, but as pressure of work rises other considerations become increasingly important, and ease of cleaning, sterilisation, and maintenance, and manpower demands can all greatly influence the choice of machine.

For these reasons the paper by Dr. GERBODE and his colleagues on p. 284 is of much interest. It is an account of the clinical use by one surgeon of two filming machines using different principles: one a fixed vertical screen, a variant of the Gibbon, developed by OSBORN[7] in San Francisco; the other the rotating-disc oxygenator devised by MELROSE[2] at the Postgraduate Medical School and introduced into the operating-theatre at Hammersmith Hospital five years ago. Dr. GERBODE had previously decided that the film oxygenator was preferable to the bubble type. Now, since "no substantial difference in mortality or morbidity or any other measurable variable could be detected", considerations of convenience, cost, and administration have made Dr. GERBODE decide on the use of the Melrose machine only in future at Stanford University Hospital. In the cases recorded the original Melrose 'Perspex' oxygenator[2] was used. The material of the oxygenator and of the discs is now to be changed to permit autoclaving and the disposal of the discs: "these requirements are judged essential for the proper maintenance and safety of an apparatus used more than five times a week." This sentence may give a clue to one of the essentials for excellence in this work: for their successful performance these complex procedures require a frequently repeated, routine, standardised technique.

The paper from Stanford University, with its account not only of the advantages of the British machine but also of the routine safe use of elective cardiac arrest—another British advance—shows that British surgery has contributed generously to the common fund of knowledge in intracardiac surgery. It illustrates too how the provision of an efficient machine does not by itself ensure successful open-heart surgery. More important now is a highly trained medical and surgical team working with unremitting diligence, and having at its disposal ample means for preoperative investigation, first-class operating-theatre equipment and accommodation, and adequate provision for the immediate postoperative recovery period and later convalescence. Dr. GERBODE and his colleagues are to be congratulated on the figures they present. The series is not long by American standards but it is long enough to be entirely convincing. It is notable that he has lost only 3 out of 14 patients treated by an intracardiac operation for the tetralogy of Fallot, and some of the other complicated defects have been very successfully dealt with. We are glad to publish a record of this project which has been brought to so satisfying a conclusion by a joint team of American and British workers.

Hæmolytic Disease of the Newborn

IN the past ten years the infant mortality in England and Wales has fallen by half, largely owing to the improved treatment of infective illness. Today 80% of neonatal deaths are due to causes, such as immaturity and congenital deformity, which cannot yet be prevented. Consequently the 350 deaths due to hæmolytic disease assume considerable importance. It can be calculated that this disease also accounts for 500 of the 16,000 stillbirths each year.

Since the discovery of the rhesus factor by LANDSTEINER and WIENER[1] in 1940, great strides have been made in the understanding and management of this disease, and it is claimed that, with early diagnosis and exchange transfusion in selected cases, over 95% of affected infants that are born alive should survive.[2,3]

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[1] Dewall, R. A., Warden, H. E., Varco, R. L., Lillehei, C. W. *Surg. Gynec. Obstet.* 1957, 104, 699.

[2] Melrose, D. G. *Brit. med. J.* 1953, ii, 57.

[3] Björk, V. O. *Acta chir. scand.* 1948, 96, suppl. 137.

[4] Dennis, C., Spreng, D. S., Jr., Nelson, G. E., Karlson, K. E., Nelson, R. M., Thomas, J. V., Eder, W. P., Varco, R. L. *Ann. Surg.* 1951, 134, 709.

[5] Gibbon, J. H., Jr. *Minn. Med.* 1954, 37, 171.

[6] Varco, R. L., Barnard, C., Dewall, R. A., Lillehei, C. W. *in* Extracorporeal Circulation. Springfield, Ill., 1957.

[7] Osborn, J. J., Gerbode, F., Perkins, H. A., Kahn, P., Braimbridge, M. *Trans. Amer. Soc. art. intern. Organs*, 1957, 3, 49.

[1] Landsteiner, K., Wiener, A. S. *Proc. Soc. exp. Biol., N.Y.* 1940, 43, 223.

[2] Allen, F. H., Jr., Diamond, L. K., Vaughan, V. C. *Amer. J. Dis. Child.* 1950, 80, 779.

[3] Walker, W., Neligan, G. A. *Brit. med. J.* 1955, i, 681.

Yet there has been no substantial fall in mortality. Indeed it is estimated that some 200 infants die needlessly each year, and this was confirmed by WALKER and MOLLISON[4] in a study of deaths attributed to hæmolytic disease in England and Wales in the years 1953 and 1955. No new knowledge is required to prevent this loss of life—only the application of existing knowledge, which is set out in a memorandum of the Central Health Services Council which is being sent to all family doctors.[5] But hæmolytic disease not only contributes to the total of fœtal and neonatal deaths: it carries important, often poignant, implications for the families concerned. Therefore, though the risks of immunisation are small, even the first pregnancy in an Rh-negative woman calls for special obstetric care.

The importance of early diagnosis is now recognised, and the memorandum outlines a policy of blood-grouping tests designed to ensure antenatal prediction. But, since this will not always be achieved, it draws attention to the early symptoms which point to the diagnosis.

The measures recommended include the Rh grouping of all pregnant women and antibody tests at 32–36 weeks of pregnancy in all found to be Rh-negative. The collection of clotted cord blood from the infants of all Rh-negative women is also recommended, since a positive Coombs test will establish a diagnosis of hæmolytic disease. (On the other hand a negative result does not exclude all forms of this disease.) An alternative plan for antenatal prediction consists in the testing of all mothers for antibodies between 32 and 36 weeks of every pregnancy. It is claimed that by this plan, as one specimen is required from every mother in every pregnancy, testing is less likely to be overlooked, while a few cases of immunisation to rare antigens are detected antenatally. Which policy is followed will depend largely on local arrangements.

The memorandum rightly points out that jaundice in the first twenty-four hours of life is to be ascribed to hæmolytic disease until proved otherwise, and demands immediate admission to hospital. This applies even if the infant is firstborn, and even when the known blood-group background appears to exclude the diagnosis. If in addition there are pallor, bruising, enlargement of the liver, or other signs, admission is urgent. Jaundice appearing after the first day of life can sometimes become so intense as to cause brain damage; therefore deep jaundice in the first week of life requires expert opinion. Hæmolytic disease due to ABO incompatibility has been recognised with increasing frequency in recent years,[6] [7] but no single test establishes the diagnosis—the Coombs test is often negative. Antenatal prediction cannot be achieved with certainty, and consequently diagnosis is usually based on the results of many tests that are not easily interpreted. The true incidence is not known. VALENTINE[8] has studied a series of infants showing jaundice in the first day of life. In all cases there was an underlying hæmolytic anæmia; in a third this was Rh hæmolytic disease of the newborn, and in the remainder hæmolytic disease due to incompatibility within the ABO groups. Some workers claim that ABO hæmolytic disease is commoner than that due to rhesus factor, but, being milder,[9] presents a less important practical problem.

As the memorandum says, results are best in units with special experience, and if a unit is to provide really effective service it must carry out the necessary tests at any hour and be able to undertake transfusion within half an hour of birth. (We hope the statement that the "interval between birth and exchange transfusion should be as brief as possible" is not misinterpreted, for such urgent treatment is required only in very severely affected infants, and in most it is better to apply this treatment between four and eight hours after birth.) A calculation based on the fatal cases in 1953 and 1955[4] showed that each hospital concerned dealt, on average, with only twelve cases a year, whereas the memorandum suggests that to maintain the required standard each unit should deal with at least fifty cases a year.

A national trial reported in 1952[10] [11] suggested that spontaneous delivery resulted in less loss of life, fœtal and neonatal, than did routine premature induction. But experience has justified premature induction in families where a preceding infant has been very severely affected or stillborn. Some workers go further and recommend induction for all cases of Rh isoimmunisation,[12-14] but such a policy should not be adopted hastily. It could prevent at most sixteen stillbirths in a hundred cases treated in this way, against which must be set the risks of induction to both mothers and infants. In fact probably only eight stillbirths would be prevented, for almost half occur before 35 weeks' gestation, the time most commonly recommended for induction. If on the other hand stillbirth could be forecast with relative certainty, induction would be justified, for there is no convincing evidence that cortisone or any other drug is of value in this condition.

There is a correlation between maternal antibody titre and severity,[15] but it is doubtful whether this is so precise as to help in the management of individual cases. WALKER[16] claims that tests on liquor amnii enable severity to be forecast. This work requires confirmation and elaboration, but, alone or together with antibody titre, such tests may prove of real practical value.

Many problems may remain, but if the recommendations of the memorandum are applied the coming years may see as big a change in the mortality of hæmolytic disease of the newborn as antibiotics have brought about in some other diseases.

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[4] Walker, W., Mollison, P. L. *Lancet*, 1957, i, 1309.
[5] Memorandum prepared by the Standing Medical Advisory Committee for the Central Health Services Council and the Ministry of Health.
[6] Crawford, H., Cutbush, M., Mollison, P. L. *Blood*, 1953, 8, 620.
[7] Rosenfield, R. E. *ibid* 1955, 10, 17.
[8] Valentine, G. H. *Amer. J. Dis. Child.* 1958, 33, 185.
[9] Vaughan, V. C. Exhibit prepared for the VIII International Congress of Pædiatrics, Copenhagen, 1956.
[10] Mollison, P. L., Walker, W. *Lancet*, 1952, i, 429.
[11] Armitage, P., Mollison, P. L. *J. Obstet. Gynæc. Brit. Emp.* 1953, 60, 605.
[12] Kelsall, G. A., Vos, G. H. *Lancet*, 1955, ii, 161.
[13] Fisher, O. D. *Brit. med. J.* 1957, i, 615.
[14] Allen, F. H., Diamond, L. K. Erythroblastosis Fetalis. Boston, 1957.
[15] Freiesleben, E. Erythroblastosis Fœtalis. Copenhagen, 1956.
[16] Walker, A. H. C. *Brit. med. J.* 1957, ii, 376.

The Development of Respirators

IN 1947 Britain had her first big epidemic of poliomyelitis There were about 600 Both-type tank respirators in the country at that time, presented by Lord NUFFIELD in 1938–39, and they were invaluable for patients with respiratory weakness; but the epidemic revealed how inadequate were the country's resources for dealing with poliomyelitis Apart from a dearth of doctors and nurses with the necessary experience, the design of respirators had failed to advance with the times, and, what was worse, many respirators had become useless from lack of maintenance. Consequently, in 1948, the design of respirators attracted much interest, and the progress of the past ten years is now reviewed in the Medical Research Council's report.[1]

Tank respirators have not changed in principle, but improvements in detail have been of great practical importance. A choice of respiratory-rates was provided, more ports were placed in the side of the tank, and an inflator was included so that artificial respiration could be continued when the patient was withdrawn from the tank for nursing care When a patient was being put into an old respirator his head had to be delivered through a small opening in the front of the tank, a very cumbersome business, which was avoided by splitting the front into an upper half which could be raised and lowered, and a lower half which was fixed This great practical advance was introduced as one of a number of modifications to the Both respirators, which were thereby given a new lease of life The principle of splitting the front of the tank was carried to its logical conclusion by the development of an "alligator" respirator, first designed in Australia by BOTH and now made by at least two manufacturers in the United Kingdom In this the whole respirator is split horizontally and hinged at the foot, so that access to the patient is easy and the respirator can be brought into action again merely by closing the lid

Cuirass respirators which fit over the abdomen and chest have also been designed, and, though as respirators they leave much to be desired, their convenience makes them useful for the patient who needs respiratory assistance for part of the day or while asleep The Tunnicliffe breathing jacket[2] is a similar device that provides more efficient artificial respiration at some cost in convenience. A rocking bed is also in production and is specially suitable for weaning from artificial respiration those patients whose diaphragms have not recovered

The fundamental novelty of this period has been the introduction of intermittent positive-pressure respiration (I.P.P.R.) in Denmark in 1952 A rubber or sometimes metal tube is inserted through a tracheotomy, and an inflatable cuff around the tube ensures a good fit in the trachea, so that foreign material in the pharynx cannot get into the lungs, and air blown into the lungs cannot escape through the nose and mouth A tracheotomy is now considered essential in any patient with paralysis of swallowing as well as of respiration, and those with experience of acute paralysis increasingly favour a tracheotomy when in doubt In the presence of a tracheotomy I.P.P.R. is, in Europe at least, the usual means of artificial respiration Many positive-pressure respirators have now been designed with many different characteristics, and the most prominent of their merits should be robustness and reliability. In I.P.P.R. each respiration resembles a miniature Valsalva manœuvre in which the intrathoracic pressure is temporarily raised There is good evidence that in very sick animals this can reduce the venous return to the heart, and that this effect can be reversed by applying negative pressure between inspirations Some of the more recent I.P.P. respirators provide a negative-pressure phase, and clinical evidence should soon be forthcoming about their efficacy

It seems likely that the stage of intensive development of breathing machines is coming to an end, and that future research will deal with the physiological state of the patient receiving artificial respiration. A wide subject for inquiry is open here, dealing not only with the exchange of oxygen and carbon dioxide in the lungs but also with the mechanics of the lungs and chest wall, with particular reference to the effects of pressure changes on the circulation

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1 Report of the Medical Research Council for the year 1956–57. H.M. Stationery Office. Cmnd. 453. 13s.

2. Spalding, J. M. K., Opie, L. Lancet, 1958, i, 613

Annotations

CANCER OF THE TONGUE

ONE of the problems that is likely to beset any surgeon interested in the operative treatment of cancer of the tongue is the small number of cases that come his way[1] This is, happily, one of the sites where the incidence of cancer seems, certainly in civilised societies, to be declining steeply—a fact difficult to reconcile with the view that cancer of the mouth and of the bronchus share tobacco as a common ætiological factor Added to this, there is an increasing tendency for all patients with mouth cancer to be channelled to the radiotherapist for their primary treatment. Accordingly it is surprising to read in the opening sentence of an appraisal of progress in surgical therapy by Danely P. Slaughter and his colleagues[2] in the University of Illinois "Somewhat over a decade has now elapsed since the surgical treatment of cancer of the tongue assumed a pre-eminent position in the over-all management of this disease." Later they admit that there is still little published evidence to sustain the claims of the surgeon in this field, but they cite unpublished data claiming a 36% five-year-cure rate in a small group of patients with regional lymph-node metastases

In the management of the tumour at the primary site the place of surgery is very much a matter of opinion; but to the view that, in general, neck metastases are best dealt with by block dissection radiotherapists usually subscribe Rather less than half the patients will be found at the outset to have no enlargement of the neck nodes, and in this type of case the expectant policy seems, in the main, to prevail, but Tailhefer,[3] from his very wide experience at the Fondation Curie, stated a strong case for prophylactic operation, claiming that his results were improved by this more energetic attack. It has now been

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1 Shedd, D. P., Schmidt, N. L., Chang, C. H. Surg. Gynec. Obstet. 1958, 106, 15

2. Southwick, H. W., Owen, J. W., Slaughter, D. P. Surgery, 1958, 43, 313

3 Tailhefer, A. Proc. R. Soc. Med. 1952, 45, 757

shown that, even where no enlarged nodes can be felt in the neck, in 40–60% of cases the nodes will be found at operation to contain microscopic metastases [3–5]

Surgical enthusiasts such as Hayes Martin [6] are now inclined to pin their faith in the cure of lingual cancer to a combined en-bloc resection of the primary tumour and the regional lymph-nodes, whether these are clinically involved or not, but he and his colleagues have displayed a not unnatural reluctance to practise prophylactic block dissection, believing that the risk of ultimate contralateral spread is 11% Slaughter [8] may be presumed to favour a more vigorous approach, since he believes the risk of such a happening to be less than 1%

Surgeons admit that this, or indeed any other, type of operation can have no place in the treatment of cancer of the posterior third of the tongue Moreover, even when surgery is undertaken under the most favourable circumstances, the chances of disappointment are considerable An apparently happy result is all too often marred by the appearance of a new primary (perhaps in 1 in 10 or more [7 8]), or a carefully conducted dissection is followed by the early appearance of seedling "recurrence" in the operation field In the prevention of this, there is perhaps relevance in the work of Southwick and Cole,[9] who in a careful study of the risk of local implantation following colon resection for cancer, showed very clearly the merit of scrupulous care in avoiding spillage of cancer cells

Consideration of the contending claims of surgery and of radiotherapy in the control of cancer of the tongue (or, for that matter, at any site in the mouth) is hampered by the lack of any good evidence on the usefulness of the two methods in comparable cases It is high time that exponents of the two approaches provided a firm answer based on shared experience

FAILURE OF DETERGENTS TO DISINFECT

IN 1935—the year in which he discovered that 'Prontosil' could cure experimental infections—Domagk described the first of a new class of surface-active chemicals with detergent and bactericidal properties The cationic members of this class are now widely used as disinfectants, and the most useful of them are the quaternary ammonium compounds It was very soon apparent that some organisms are sensitive to the sulphonamides and others resistant, but even now it is not always realised that there are similar differences in sensitivity of different bacteria to the action of the quaternary ammonium disinfectants Gram-positive cocci are much more sensitive to these agents than are gram-negative bacilli, *Pseudomonas pyocyanea* is relatively resistant In practice these disinfectants are used at concentrations which should suffice to kill even less sensitive bacteria, but under working conditions the effective concentration or the time of exposure may be so reduced that *Ps pyocyanea* will not be destroyed Plotkin and Austrian [10] have described the consequences of such a failure in disinfection

Fifteen patients in a New York hospital developed septicæmia after receiving intravenous transfusions Blood-cultures from every patient yielded the same organism—an unusual bacillus closely related to *Ps pyocyanea* This finding prompted a full investigation of all materials used in intravenous transfusions, and it was found that swabs for disinfecting the skin before injection, which were stored in disinfectant, were contaminated with the same organism The disinfectant was a 0 1% solution of 'Zephiran', a quaternary ammonium compound widely used in North America Before each intravenous injection the skin had been smeared with what was in effect a culture of live bacteria It is known that cationic detergents are adsorbed readily to cotton fibres,[11] and this appears to have been the way in which the concentration of zephiran was reduced below that necessary to kill *Ps pyocyanea* and related bacteria Last year Keown et al [12] reported five deaths from *Ps pyocyanea* septicæmia after cardiac operations, the source of the infection being a heart-lung machine supposedly sterilised with 0 1% zephiran [12] Lowbury cultured *Ps pyocyanea* from bottles of 1% cetrimide in use in a British hospital [13] The organisms survived in the corks, and substitution of screw-caps for corks in disinfectant bottles greatly reduced the number of *Ps pyocyanea* infections in this particular hospital Anderson and Keynes [14] have shown that extraction of the cork releases a shower of infected cork dust into the bottle Organisms from this dust may cause wound infection if the disinfectant is used immediately after being poured out—before the organism has been exposed to disinfectant long enough to be killed

Practical lessons may be learnt from these mishaps Disinfectants should not be dispensed in bottles with corks Gauze and cotton-wool swabs should not be sterilised and stored in disinfectant but should be sterilised in a pressure-steam steriliser Complex apparatus which cannot be heated is probably best sterilised with ethylene-oxide gas [15] Quaternary ammonium compounds are not very satisfactory skin disinfectants As we pointed out some years ago, the most effective disinfectant for this purpose is still 2% iodine in 70% spirit [16]

In short, quaternary ammonium disinfectants should be used with some discretion, in the knowledge that in their action on bacteria they resemble the sulphonamides more than the autoclave

HOMOTRANSPLANTATION OF THYROID IN UNIOVULAR TWINS

WHEN it became evident that myxœdema and cretinism were due to thyroid deficiency the first proposal for treatment was that a healthy thyroid should be transplanted into the affected person Horsley [17] in 1890 suggested that the thyroid of a sheep might be used for this purpose, and this suggestion was carried out by Bettencourt and Serrano [18] in the same year Horsley [19] recorded that even earlier both Bircher and Kocher had treated cachexia strumipriva by implanting fragments of goitre from another person into the patient's abdominal cavity We now know that attempts to graft tissue from another species, or even from another human being, are immunologically futile

As would be predicted, these early transplantation experiments were followed by only temporary clinical improvement, and their only importance is that they led directly to Murray's demonstration of the effectiveness of thyroid extract in the treatment of myxœdema When tablets of dried thyroid extract came into common use, interest in the possibilities of transplantation lapsed It seemed difficult to imagine any treatment simpler and

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4 Lyall, D , Schetlin, C F *Ann Surg* 1952, 135, 489
5 Roux-Berger, J L , Baud, M , Courtial, J *Mém Acad Chir* 75, 120
6 Martin, H Surgery of Head and Neck Tumours London, 1958
7 Wood, C A P , Boag, J W Researches on the Radiotherapy of Oral Cancer *Spec Rep Ser med Res Coun Lond* 1950, no 267
8 Slaughter, D P , Southwick, H W Smejkal, W F *Cancer*, 1953 6, 963
9 Southwick, H W , Cole, W H *Surg Clin N Amer* 1955, 35, 1363 See *Lancet*, 1956, i, 944
10 Plotkin, S A , Austrian, R *Amer J med Sci* 1958, 235, 621
11 Glassman, H N *Bact Rev* 1948, 12, 105
12 Keown, K K , Gilman, R A , Bailey, C P *J Amer med Ass* 1957, 165, 781
13 Lowbury, E J L *Brit J industr Med* 1951, 8, 22
14 Anderson, K , Keynes, R *Brit med J* 1958, ii, 274
15 Skeehan, R A , King, J H , Kaye, S *Amer J Ophthal* 1956, 42, 424
16 *Lancet*, 1952, i, 250
17 Horsley, V *Brit med J* 1890, i, 287
18 *Sem Med* 1890, 10, 294
19 Horsley, V *Brit med J* 1890, ii, 201

more completely effective than oral replacement therapy Yet fatal cases of myxœdema still occur [20], the usual sequence of events seems to be that patients correctly diagnosed and treated in the first instance become careless in time about taking their tablets and eventually pass into a state of severe myxœdema which is therapeutically irreversible For the most part such cases have occurred in people living alone with no-one at hand to remind them of the need for taking tablets It is evident that a successful thyroid graft would be a complete protection against this unhappy sequence of events, and it therefore seems worth reviewing again the possibilities of transplantation

The work of P B Medawar and his school on immunological tolerance has shown that homotransplants have no hope of survival unless the recipient has been prepared by the injection of the relevant antigens during fœtal or very early postnatal life How early this would have to be in man is uncertain, but a homotransplant might possibly survive if implanted in the first few weeks of life It is unfortunately difficult to diagnose cretinism at any age less than about 3 months, but the combination of astute clinical observation and modern tests of thyroid function might establish the diagnosis in a few isolated cases If this could be done before the patient reached the age of 1 month, transplantation of a piece of thyroid from another person might be worth attempting

At any later age homotransplants will certainly fail to take, with the single exception of one taken from an identical twin Fortunately when one uniovular twin is cretinous the other is usually normal, and this was so in the case described by Harnack et al [21] The healthy twin, Marina, had a normal uptake of radio-iodine, but her cretinous sister, Christiane, had only a trivial uptake in a minute fragment of thyroid tissue at the base of the tongue When the twins were 7½ years old the greater part of one lobe of Marina's thyroid was removed at operation and inserted in two pieces in Christiane's neck, one on each side, deep to the sternomastoids The early clinical effects were not striking, and three months after the operation Christiane again required oral thyroid treatment But a year later, thyroid was stopped without an immediate decline into hypothyroidism. Radio-iodine tests after administration of thyroid-stimulating hormone showed that the child now had useful, though still greatly subnormal, thyroid function It seems likely that the bulk of the implanted thyroid must have died shortly after the operation, but that enough remained for regeneration to occur Further observation will be required before we know whether the fragments will supply all the child's requirements of hormone

ENTEROPATHOGENIC ORPHANS?

IN 1956 a conference was held in New York on Viruses in Search of Disease [22]—an unusual topic It is, in fact, an important one, because so many viruses are now being isolated from the intestines of healthy people 47 of these "enteroviruses" [23] are known—3 types of poliovirus, 19 of Coxsackie A, 5 of Coxsackie B, and 20 of the enteric cytopathogenic human orphan (ECHO) group —and there is no reason to think that the list will end here Some are already firmly associated with disease poliovirus, Coxsackie virus, and some types of ECHO virus which cause aseptic meningitis Ramos-Alvarez and Sabin [24] have studied their association with summer diarrhœa of infants and very young children

They describe an epidemiological study in which a comparison was made between the viruses and bacteria isolated from the fæces of 153 children with diarrhœa and of 100 healthy children of the same age, district, and socioeconomic background Material from rectal swabs was used to inoculate monkey-kidney tissue cultures and newborn mice Cultures were also made for pathogenic bacteria, and paired sera were tested from 24 of the patients who had positive stools While enteroviruses were isolated from 20% of the healthy children, they were present in about 50% of those with diarrhœa This difference lay largely with the ECHO viruses, which were six times commoner in the test group than in the controls The prevalence of poliovirus and Coxsackie virus (about 3%) was the same in both groups 7% of the patients carried salmonella or shigella, which were not isolated from the healthy children, but there was no significant difference in the rates for pathogenic strains of *Escherichia coli* In all the cases where the serum was examined there was a rise in titre to the virus which was isolated from the rectal swab This proves that the virus in the fæces was causing an active infection when the child was ill, but does not prove that this infection was the cause of the symptoms

The evidence in this paper certainly suggests that the ECHO viruses may be a cause of summer diarrhœa But great care has to be taken before claiming that an enterovirus is a cause of disease These agents are isolated so often from healthy children that it would be surprising if they were not found also in the fæces of those with diarrhœa from other causes Mixed infections may occur, or infection with agents which we cannot detect by existing techniques It is difficult to exclude completely the possibility that viruses may arise from the cells or serum used in the tissue culture Yet another difficulty lies in the nature of the disease As Ramos-Alvarez and Sabin remark, "Summer diarrhœa of very young children is not a clinical entity but rather a consequence of transitory infection with a large variety of bacterial and viral pathogens" Even in the ECHO group no particular type seems to be associated with the disease In this study the viruses isolated were distributed among thirteen different serological types But Ramos-Alvarez and Sabin cite an outbreak of diarrhœa among infants in hospital described by Eichenwald et al [25] which was apparently caused solely by ECHO virus type 18 Possibly when we know more about the group some epidemiological pattern may emerge, as it has with the staphylococci and pathogenic *Esch coli*

The first report of the committee on the ECHO viruses in 1955 [26] stated that, as soon as one of these viruses was established as the cause of a clinically distinct disease, it should be removed from the group—which is probably a heterogeneous one anyway Although associations are being demonstrated between ECHO viruses and disease, they do not appear to be clear-cut enough to justify the removal of these agents from the "orphanage" The name ECHO has been acquiring a meaning in its own right as the meaning of the initials is forgotten [27], it seems likely that the name "orphan viruses", applied by Duran-Reynals "at a moment of conviviality",[26] will persist

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[20] *Lancet*, 1956, ii, 768
[21] Harnack, G A., Horst, W, Lenz, W, Zukschwerdt, L *German med Monthly* 1958, 3, 172
[22] *Ann. N Y Acad Sci* 1957, 67, 209
[23] Committee on Enteroviruses of the National Foundation for Infantile Paralysis *Amer J publ Hlth* 1957, 47, 1556
[24] Ramos-Alvarez, M., Sabin, A B *J Amer med Ass* 1958, 167, 147
[25] Eichenwald, H. F, Ababio, A., Arky, A. M, Hartman, A. P *ibid* 1958, 166, 1563
[26] Committee on ECHO viruses of the National Foundation for Infantile Paralysis *Science*, 1955, 122, 1187
[27] Andrewes, C. H., Sneath, P H A *Nature, Lond* 1958, 182, 12.

Occasional Survey

BIOCHEMICAL CONCEPTS OF SCHIZOPHRENIA *

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THE demonstration of the organic basis of general paralysis led, about fifty years ago, to the hope that schizophrenia might also prove to be caused by some easily distinguishable organic agent or condition The discovery that psychoses or mental deficiency could be caused by avitaminosis, hormonal imbalance, and specific disorders of metabolism, such as phenylketonuria, lent weight to the belief that schizophrenia might also be due to some metabolic or endocrine disorder, but the persistent failure to demonstrate any such organic basis led to a slackening of the momentum behind this approach and to the gradual dominance of the belief, among psychiatrists in North America at any rate, that the ætiology of schizophrenia was essentially psychological

A physiological interpretation of this psychological hypothesis may be put as follows everyone would agree that severe emotional trauma can lead to behavioural disturbances The psychological theories hold that schizophrenia may be explained by a logical extension of this, coloured by the discovery that emotional and other allied psychological factors can continue to interact and to act as causal agents when they are no longer present in consciousness, for this is what the Freudian theory of the unconscious amounts to Psychoanalysis holds that the causes of the illness lie in faulty early training and interpersonal relationship Its physiological basis is supposed merely to consist of those mechanisms whereby *any* past experience affects present emotional experience, motivation, and behaviour, reacting in this case to an involved and scarifying series of noxious experiences The warping of the child's psychological development is held to be a sufficient explanation of the adult schizophrenic The schizophrenic is withdrawn *because* the early environment forced the child to withdraw, and no specific metabolic fault is held to be involved

However, we now have a considerable body of evidence against this hypothesis, for organic changes have been discovered in schizophrenia that are certainly relevant to its ætiology, and progress has been made in constructing plausible hypotheses to explain these biochemical and pathological findings, but this does not lead us to reject the importance of psychological factors, as we shall see

The evidence for a genetic cause of schizophrenia is now generally agreed to be overwhelming, although the exact details may not yet be known Kallmann (1953) has accumulated a large body of evidence favouring the hypothesis that single-factor inheritance of the recessive type is the genetic cause of schizophrenia There are also more specific physiological findings The metabolic theories of schizophrenia have been focused on the idea of some cerebral toxin produced by faulty metabolism Equally possible are the lack of a necessary factor and the imbalance between two complementary mechanisms

An early proponent of such a view was Jung (cited by Osmond 1957) with his " toxin X "

Mann and Quastel (1940) proposed that a toxic amine might be responsible, and a popular idea of that time was that toxic amines from the gut might be involved—an idea that did not prove fruitful in this field but has found application in another following the work of Sherlock et al (1954), who showed that venous blood derived from the gut and bypassing the liver can produce psychotic effects

Buscaino (1952) introduced the concept of a toxic indole as causing schizophrenia, which idea is again fashionable

Broad Biochemical Investigations

In the absence of any specific directing hypothesis a large number of biochemical investigations were made on a wide front in the hope of turning up some clue that might suggest the cause Many of these reports were negative or contradictory, and the validity of others was doubtful either because the tests used were unreliable or because the findings might well be explained by the poor diet, concomitant medication, lack of motility, &c, of schizophrenics

Out of all this work the only findings that seem reliable are as follows

(1) *Liver function* —Richter (1957) states that there appears to be some impairment of liver function in schizophrenics as a whole, but there is no evidence that it is an invariable or obligatory concomitant However, Richter emphasises the possibility that different enzyme systems in the liver may be affected to different degrees, and concludes that we cannot yet exclude the possibility that in schizophrenics some of the functions of the liver may be seriously impaired

(2) *Toxicity of body fluids* —The blood of schizophrenics has been reported to be toxic to tadpoles (Fischer 1953) and to fibroblasts grown in tissue culture (Fedoroff and Hoffer 1956), but the latter workers find a similar degree of toxicity in patients undergoing surgery, suggesting that a non-specific response to stress of the kind described below may be involved Reider (1957), using Witt's elegant spider-web technique, has shown that extracts from schizophrenic urine produce significant abnormalities in the web-spinning behaviour of spiders similar to those produced by hallucinogens

(3) *Reaction to stress* —Various measurements have been made of the response (pulse-rate, blood-pressure, skin circulation, and response to adrenaline) to stress (Finkelman and Stephens 1936, Pfister 1938) These show that chronic schizophrenics are less reactive than healthy people Increased excretion of 17-ketosteroids has been found only in paranoid schizophrenia (Sands 1957)

(4) *Circulatory system* —Careful observations have shown that schizophrenics exhibit a mild but consistent degree of hypotension and a constriction of the small arterioles of the skin, leading to cyanosis (Shattock 1950) This is also evidence of a disorder of capillary structure (Lovett Doust 1955)

(5) *Metabolism of nitrogen* —Nitrogen is retained in recurrent catatonia, but this condition is rare and may not be related ætiologically to the bulk of cases of schizophrenia

(6) *Metabolism of phosphorus* —Örström and Skaug (1950) found a diminished turnover of adenosine triphosphate in schizophrenics, and Örström (1951) reported a higher content of phosphoglycollic acid in their red blood-cells

(7) *Abnormalities in brain* —This work is still in its early stages, but Ashby (1950) has reported that the activity of carbonic anhydrase is abnormal in schizophrenia Normally the activity of this enzyme is greatest in the occipital cortex and least in the temporal region, but in schizophrenia the normal topographical pattern was obliterated, except in some early cases, where there was a reduction in the frontal region Birkhauser (1941) reported a lower activity of monoamine oxidase than normal in the pallidum of schizophrenic subjects

(8) *Homœostasis* —If a large series of measurements is made of basal metabolic rate, circulation-rate, body temperature,

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* Based on seminars held at the University of Iowa, March 1, 1958, and at Emory University, April 29, 1958

excretion of 17-ketosteroids, thyroid activity, and water metabolism in schizophrenics and in healthy people, it will be found that the variance of these readings will be greater in the schizophrenics This suggests that a concomitant of schizophrenia is some disorder of homœostasis

(9) *Other disorders* have been reported, such as disordered excretion of various substances in the urine—e g , sulphur compounds (Koch and Mann 1909), phenolic derivatives (Richter 1957), indoles (Riegelhaupt 1956), imidazoles (Stewart 1930), and aromatic substances (McGeer et al 1956)—but this very variety suggests that these compounds arise from increased bacterial action in the gut from some local cause such as stasis rather than a specific metabolism of schizophrenia

In summary, therefore, those investigations not directed by a specific hypothesis lead only to the certain deductions of a disordered response to stress, a disordered homœostasis, a probably non-specific toxicity of body fluids, a disorder of nitrogen metabolism in a certain rare kind of schizophrenia, and specific disorders of phosphorus metabolism and of cerebral carbonic-anhydrase and amine oxidase function These empirical findings do not suggest any specific theory but only that the biochemical mechanisms of the response to stress and of homœostasis are involved

First Specific Biochemical Theory

The first specific[1] biochemical theory of schizophrenia was put forward by Osmond and Smythies (1952) and was stated in a more specific form by Hoffer et al (1954)

Search for Toxic Metabolite

These workers applied a form of Koch's postulates adapted to a metabolic illness These postulates require us to isolate from schizophrenics a metabolite which, injected into healthy people, would reproduce the symptoms of schizophrenia This metabolite should either be found de novo in schizophrenics, or at least in significantly larger amounts in schizophrenics than in healthy people, or possibly the schizophrenic may be abnormally sensitive to the metabolite Contributory evidence should be obtained by showing other toxic properties of the metabolite or by testing for its presence in a deductive manner

But what metabolic fault should one look for in schizophrenia? There are millions of possible faults—which one should we choose? We approached this problem by asking a series of questions The first was What known chemicals are there that produce in healthy people effects closest to the symptoms of schizophrenia? We delineated a class of chemicals, including mescaline and lysergic acid diethylamide (L S D), that had this property and we called them "hallucinogens" We did not claim that these compounds produce exactly the signs and symptoms of schizophrenia The differences in temporal and situational factors will always preclude the exact matching of an experimental and a natural psychosis However, for our purpose what was required was the closest known analogy

We next asked which of these substances or any substance nearly related thereto could conceivably be formed in bodily metabolism, and we pointed to the close chemical relationship between mescaline and adrenaline, which suggested that derivatives of adrenaline might be strong candidates for the role of "M substance"—the mescaline-like toxin of schizophrenia Our hypothesis does not necessarily involve indoles except in so far that certain metabolites of adrenaline are indoles, our hypothesis is specifically directed towards metabolites of adrenaline and allied compounds

Harley-Mason (cited by Osmond and Smythies 1952) suggested one specific mechanism whereby a closer mescaline analogue than adrenaline could be produced in the body—i e , methylation of the phenolic groups of adrenaline—a reaction that Axelrod (1957) has found taking place in the body The finding by Resnick et al (1958) that adrenaline is *predominantly* detoxified by *o*-methylation in humans brings Harley-Mason's hypothesis of an excessive methylation back into prominence A possible fault might be the production in schizophrenia of the possibly psychotomimetic dimethoxy derivative of adrenaline The comparative amount of *o*-methylation in schizophrenics and normals should be measured a lesser degree in schizophrenics might suggest that some of the adrenaline was being metabolised by the adrenochrome pathway This hypothesis could easily be tested

Adrenochrome

Dr Eric Asquith, an anæsthetist at Regina General Hospital, told us that he had obtained psychotic reactions by giving patients injections of "pink adrenaline," which is a red mixture of oxidised products of adrenaline Since then Hoffer and Osmond (1958) have made an extensive study of a psychosis lasting a month and produced by the self-administration of "pink adrenaline" (to which adrenaline turns slowly on mere exposure to the air) for this length of time by an asthmatic; and H E Himwich (personal communication) has told us that he has observed an injection of adrenaline 1 mg to produce severe temporary personality changes of a paranoid type in a healthy person So we suggested that M substance might be adrenochrome, adrenolutine, or some other close relation among the many closely allied immediate oxidation products of adrenaline This hypothesis led to a number of experiments and observations

Some solutions of oxidation products of adrenaline have been reported to produce psychological disturbances in healthy volunteers, whereas others did not The difficulty here is that adrenochrome is very unstable and extremely reactive Thus in most cases it is probable that a mixture of substance has been injected and that adrenochrome is quickly changed into other substances once it gets into the body

Hoffer (1957a) has published observations on the more stable adrenolutine (trihydroxy N-methyl indole, an isomer of adrenochrome) By a double-blind technique he tried to determine which persons had had the adrenolutine and which had had the placebo

This he was unable to do at first as the P value of his result was only 0 1 In a later experiment (Hoffer 1957b) he succeeded in doing this with a P value of 0 02 However, in a third experiment (Hoffer 1957b) done in the three months following the last experiment, he again failed to make a significant prediction This probably means that the adrenolutine had deteriorated by this time, but of course, strictly speaking, chi-square should always be calculated for the whole of such a series to avoid the charge of selection of data Chi-square for the whole series did not reach significant values (P=0 2), but the majority of successful predictions came during the first month, thus suggesting a deterioration of the adrenolutine Hoffer is repeating these experiments, using a pure sample of adrenolutine

Another difficulty is one common to all tests that may be made of any drug to see whether it produces symptoms resembling psychosis, and that is the design of the experiment.

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[1] Where a single compound, or a *small* group of compounds, or a specific biochemical mechanism is specifically implicated in the causation of schizophrenia

Pilot experiments will be needed to test the range of the apparently effective dose, to look for the type of response to expect, and to spot any undesirable complications The actual evaluation of psychotomimetic properties of a drug then depends on a properly designed double-blind experiment in view of what we now know of the extraordinary range of placebo reactions that can occur (Trouton 1958) Now that the pure forms of these compounds are, through the efforts of Heacock et al (1958), at last available, we can proceed to properly designed evaluation of stable compounds in the adrenaline oxidation series

Gastaldi et al (1957) were unable to produce such symptoms with pure adrenochrome, but they did not appear to use the careful psychological testing methods of Hoffer (1957 and b)

We found no change in behaviour in mice, even after such a large intraperitoneal dose as 40 mg per kg of body-weight, and S Martens (personal communication) has found none in monkeys

Species differences are important in this field, however, particularly in the case of those higher social, intellectual, and emotional functions that are affected in schizophrenia and hardly play any prominent part in the lives of mice or even monkeys Possibly the enzyme systems that control these higher functions may hardly be developed in the lower mammals Thus evidence from non-human sources about substances producing symptoms resembling psychosis needs to be assessed with caution However, it is quite possible that adrenochrome is not such a substance but that one of its precursors or derivatives may be

The work of Professor P Holtz and Dr G Taubmann (personal communication) has thrown some light on this They have found that freshly prepared adrenochrome does not produce symptoms resembling psychosis, but, if it is first oxidised by shaking with normal human serum in air, the resultant liquid (deproteinised) will produce symptoms of psychosis if given sublingually Furthermore, pure adrenochrome does not inhibit glutamic-acid decarboxylase whereas the oxidised form is a potent inhibitor of this important enzyme which produces the aminoacid G A B A (γ-aminobutyric acid) thought to be concerned with synaptic inhibition in the brain This is the first confirmation to date of the work of the Saskatchewan group on humans

Schwarz et al (1956) report that intraventricular adrenochrome produces a drowsy state in monkeys with insensitivity to painful stimuli, as does intraventricular adrenaline, and Witt (1954) has produced abnormalities in the web-spinning of spiders by its use

Adrenochrome is certainly highly active chemically Meyerhof and Randall (1948) showed that it strongly inhibits the important enzymes hexokinase and phosphohexokinase concerned in the metabolism of glucose in the brain, and Abood and Romanchek (1957) have shown that it has "a formidable effect on phosphorylation processes"

Adrenochrome is so unstable and so biologically active that, if it is introduced into the blood-stream, none may survive unchanged by the time it reaches the brain

Furthermore there is a general point concerning the relevance of the blood-levels of internally produced derivatives of adrenaline to psychosis If noradrenaline and adrenaline are both neurohumours, mechanisms for their formation and destruction must be present close to their sites of action in the brain substance If, therefore, the metabolism of these substances leads to the production of toxic substances, these latter can be produced locally in the brain and there give rise to symptoms resembling psychosis without having to enter the blood, or the end-product that does appear in the blood may be non-toxic An allied argument has been presented by Shore et al (1957a)

Clearly, much more basic work is needed on the metabolism of adrenaline both in the brain and in the rest of the body in both healthy people and schizophrenics There is, however, some indirect evidence

Lea (1955) argued that, since adrenochrome is an antihistamine, if schizophrenics had large amounts of circulating adrenochrome in their bodies they should be less susceptible to allergic conditions He made a careful study of schizophrenics in British Army records, using head-injured patients as controls, and showed that there was a highly significant deficiency ($P > 0\ 001$) of schizophrenics with allergic conditions A similar finding has been published by Ehrentheil (1957), Swartz and Semrad (1951), and other workers in America This finding also fits in with Lucy's (1954) observation that the histamine tolerance of schizophrenics is increased

This cannot, however, be necessarily taken as evidence that adrenochrome is the responsible agent in schizophrenia, because it may merely represent an end-product of the disordered cerebral metabolism of adrenaline, and some such earlier product as the quinone derivative of adrenaline (2-methylamino-ethanol-quinone) might be the actual toxin, as described above Rinkel et al (1954) suggest that adrenoxine, yet another oxidative product of adrenaline, is the responsible toxin

More recent work, however, runs against this hypothesis Resnick et al (1958) show that, in man, practically all the infused β-labelled adrenaline can be recovered from the urine mostly as 3-methoxy-4-hydroxy-mandelic acid

Holland et al (1958) measured equilibrium plasma concentrations of adrenaline and noradrenaline and detected no difference between healthy people and schizophrenics as regards the rates of utilisation of circulating adrenaline and noradrenaline

Axelrod (1958) has been unable to detect any adrenochrome in normal or schizophrenic plasma

Supportive evidence, however, for the hypothesis of deranged function of adrenaline in schizophrenics comes from Walaszek et al (1958), who found that the serum of schizophrenics either abolished or reversed the systemic vasopressor response produced by the topical application of adrenaline to the exposed cerebral cortex, the serum of healthy people had no such effect They also found that rabbit brain premedicated with the serum of schizophrenics gave significantly higher values for adrenaline and noradrenaline than did similar assays of brain tissue from rabbits pretreated with serum from healthy people

Taraxein

The next development came from Heath's group in New Orleans Following our suggestions about the possible role of oxidation products of adrenaline in schizophrenia, these workers supposed that the serum of schizophrenics might oxidise adrenaline faster than does the serum of healthy people Leach and Heath (1956) confirmed this hypothesis experimentally, and Hoffer and Kenyon (1957) showed that the substance produced was adrenolutine Heath et al (1958) by a brilliant series of researches isolated a factor, present in the serum of schizophrenics but absent from that of healthy people, which, they reported, would reproduce clearcut symptoms of schizophrenia when injected into healthy people They called this factor taraxein The films showing these reactions are certainly impressive, but confirmation by an independent group is still required

What is the chemical nature of taraxein? Heath's group also showed that blood-ceruloplasmin levels are raised in schizophrenia to such values as are found in pregnancy, chronic sepsis, and terminal carcinomatosis

The level of blood-ceruloplasmin (measured by blood-copper) shows a positive correlation with the spontaneous remission-rate and a negative correlation with the chronicity of schizophrenia As psychotic patients begin to improve clinically, the blood-copper level falls rapidly So, clearly, the raising of the blood-ceruloplasmin level cannot be the cause of the schizophrenic reaction In any case the high levels of blood-ceruloplasmin are also found in the other conditions of chronic somatic stress listed above Hence ceruloplasmin appears to provide some protective mechanism against this stress, possibly as a method of detoxifying the excess of adrenaline produced in a severe reaction to stress

The raised blood-ceruloplasmin of schizophrenics has been confirmed by Abood et al (1957) There is, however, considerable overlap with normals and Ostfeld et al (1958) showed that ceruloplasmin levels are raised by any state of emotional stress

But the relation of taraxein to ceruloplasmin remains obscure, beyond the fact that taraxein is probably a globulin, according to S Martens (personal communication), who has also found that adrenolutine in large doses produces a state similar to that evoked by taraxein In animals premedication with taraxein or L S D potentiates the effect of adrenolutine about tenfold This suggests that these substances either interfere with the breakdown of adrenolutine or its binding, or sensitise the tissues to the action of adrenolutine much as L S D potentiates the effect of adrenaline

Hoagland (1957) reports important biochemical similarities between schizophrenics and healthy people who have taken L S D Schizophrenics react to corticotrophin by a smaller increase than do healthy people in their excretion of 17-ketosteroids, sodium, potassium, and uric acid but by a larger increase in that of inorganic phosphate Healthy people show similar changes after the administration of L S D Hoagland therefore suggests that both L S D and the toxic metabolite of schizophrenia facilitate the conjugation of inorganic phosphorus with organic substances or slow the rate of turnover of phosphorus This suggestion is supported by the observation of Abood and Romanchek (1957) that adrenochrome has a formidable effect on phosphorylation processes Furthermore Hoagland (1957) reports that schizophrenics do not excrete adrenaline after the administration of L S D whereas healthy people do

Second Specific Biochemical Theory

The second specific biochemical theory of schizophrenia was put forward by Woolley and Shaw (1954) This was based on the observation that L S D , which is the most powerful hallucinogen known, is also a potent antagonist of serotonin when tested on smooth muscle, blood-pressure, &c Therefore Woolley and Shaw supposed that its hallucinogenic effects might be due to its interference with the action of serotonin in the brain

Serotonin has been discovered in the brain, particularly in the phylogenetically older areas, such as the hypothalamus (Bogdanski et al 1957, Costa and Aprison 1958) The enzyme 5-hydroxytryptophan decarboxylase, which synthesises serotonin, and monoamine oxidase, which destroys it, have also been found in the brain, also in highest concentration in the hypothalamic areas Brodie and Shore (1957) and others have suggested that serotonin is an important chemical mediator in the nervous system It is therefore understandable that either an excess of serotonin or a lack of it might lead to mental dysfunction If serotonin acts by depolarisation of nerve-cells, too much of it would lead to a permanent state of depolarisation, and thus no impulses could be transmitted, and too little of it would lead again to an absence of impulses

Other findings are also relevant to this hypothesis An early criticism was that the brom derivative of L S D ('B O L 148') is also an antagonist of serotonin but is not hallucinogenic Chlorpromazine is also a powerful anti-serotonin and, so far from being hallucinogenic, is powerfully antihallucinogenic However, it is of course possible that L S D and B O L may have the same effect on the peripheral reactions and a different effect on the central nervous system

A second criticism has a quantitative basis It has been calculated that during the period of hallucinations in man there is in the brain less than 0 000001 mg of L S D per g of brain substance (Axelrod et al 1957), and in this very low concentration L S D actually potentiates serotonin (Costa 1956) However, the possibility remains that L S D produces some of its mental effects by potentiating serotonin rather than by antagonising it

Serotonin does not produce any effects on injection but it probably crosses the blood-brain barrier only very slowly The precursor of serotonin (5-hydroxytryptophan) can be given instead, and this readily crosses the blood-brain barrier and is transformed into serotonin in the brain and causes a great rise in the brain-serotonin level It also causes in dogs behaviour disturbances similar to those caused by L S D (Udenfriend et al 1956)

Bufotenin, which is chemically very closely related to serotonin and is pharmacologically almost indistinguishable from it, is a very potent hallucinogen and produces symptoms resembling psychosis There is an important difference, however, in that 5-hydroxytryptophan produces a sleep type of electroencephalogram and L S D an arousal type, indicating different methods of action of the two drugs (Costa and Rinaldi 1958) In other words, it is unlikely that they both work merely by raising the brain-serotonin level

Another aspect of this problem has been emphasised by Costa (1956), who has found that the power of many drugs to produce symptoms resembling psychosis quantitatively parallels their power to potentiate the reaction of the cat's nictitating membrane to adrenaline Furthermore, bufotenin has a much stronger effect than serotonin, and lysergic acid diethylamide sixty-five times the effect of B O L

Another argument in favour of the serotonin hypothesis is the fact that reserpine depletes the brain of its store of serotonin (Shore et al 1957b), and its tranquillising effect parallels in time the time course of this depletion and not the time course of the mere presence of reserpine in the brain Reserpine actually frees serotonin from a bound form to a free form in the brain, and this free form is rapidly metabolised by amine oxidase L S D inhibits the destruction of serotonin by amine oxidase (Hoagland 1957) and thus may cause the brain-serotonin level to rise, although a rise in the level of the bound form may be necessary for the production of symptoms resembling psychosis However, reserpine can be counteracted by giving dopamine and thus restoring the levels of catechol amines (Carlsson et al 1957) but not by giving 5-hydroxytryptophan alone (and thus restoring the level of serotonin) The effect of these two precursors show summation if they are given together This suggests that the effects of reserpine are mediated both through its effects on brain serotonin and catechol amines but more strongly through the latter

Zeller (1958) has reported a derangement of tryptophan metabolism in schizophrenia In a tryptophan-load test schizophrenics will excrete more xanthurenic acid and less 5-hydroxyindoleacetic acid than normals The difference was statistically significant. Serotonin is a derivative of tryptophan

Third Specific Biochemical Theory

The third specific biochemical theory of schizophrenia implicates the metabolism of acetylcholine in the brain Different aspects of this hypothesis have been put forward by Hoffer (1957a) and Pfeiffer and Jenney (1957) The latter argue from the facts that (1) many tranquillisers have persistent acetylcholine-like effects, (2) drugs which show the nicotinic properties of acetylcholine—e g, di-isopropyl fluorophosphate—make schizophrenics worse, and (3) drugs which show muscarinic effects—e g, arecoline—make them better Therefore drugs which alter the level and activity of acetylcholine in the brain can alter the clinical state of the schizophrenic, and low levels of acetylcholine might be expected in schizophrenic brains Administration of a precursor of acetylcholine has been reported to benefit chronic schizophrenics (Pfeiffer et al 1957) A disorder of acetylcholine function may be secondary to an upset of adrenaline function, because adrenochrome is an anti-cholinesterase (Hoffer 1957a) One can also speculate that the metabolism of serotonin may also give rise to drugs which produce symptoms resembling psychosis, because its oxidation gives rise to a red substance chemically allied to adrenochrome

Patzig and Block (1953) have found that injected mescaline (incorporating ^{14}C) is rapidly bound to liver protein and that, during the period (in mice) corresponding in time to the period of hallucination in man, very little mescaline was found in the brain They suggested that this transformed mescaline was the cause of the mental symptoms, and that schizophrenia might be associated with a faulty hepatic detoxication of endogenous toxins The absorption of the mescaline on to liver protein may block sites of detoxication of some endogenously produced toxin Working on this hypothesis Harley-Mason et al (1957) looked for metabolites either of mescaline or of abnormal bodily metabolism in the urine of healthy volunteers who had taken mescaline A new metabolite of mescaline (3 methoxy, 4–5 dihydroxyphenylacetic acid) was discovered but was thought unlikely to cause mescaline psychosis

Conclusion

The general concept of schizophrenia that arises from the facts at present at our disposal is that it is a genetically determined disorder of the metabolism of the neurohumours of the central nervous system—noradrenaline and adrenaline, serotonin and/or acetylcholine The cause of schizophrenia may be a primary genetically determined fault in one of these systems—e g, the production of toxic oxidative metabolites of adrenaline, which would disrupt the normal functions of the brain through their actions on key enzyme systems, such as hexokinase and phosphorylation mechanisms, as well as their actions on the metabolism of the other neurohumours, such as the action of adrenochrome on cholinesterase On the other hand, the different clinical pictures of schizophrenia may result from different genetically determined faults in more than one of these systems, producing, through the interaction of these systems, allied clinical pictures

There remain two advantages of the concept of the primary fault in the metabolism of adrenaline The clinical course of schizophrenia strongly suggests by its indolent chronicity the operation of a vicious circle The adrenaline-derivative hypothesis offers the possibility of two such vicious circles (see below), it also offers an explanation of the clinical correlation of the disease with stress of some kind

It is well recognised that the onset of schizophrenia is commonly linked to some specific stress, perhaps a battle stress, or emotional, interpersonal, or biological stress Such stress situations will be associated with a chronic overactivity of the sympathetic system, and it is to be expected that any latent faults in this system would become apparent at this time

This is where the first vicious circle comes in The production, by the metabolism of adrenaline, of end-products which cause symptoms resembling psychosis will lead to further stress because the experience of the effects of these end-products is also stressful, as anyone who has experienced the appalling effects of mescaline and sympathetic overactivity combined, as I have, can testify This further stress will lead to the production of further activity in the sympathetic nervous system and thus more adrenaline, more toxic breakdown products of this adrenaline, and so, in turn, more stress, thus constituting the vicious circle

The second possible vicious circle is constituted by the anti-cholinesterase effect of adrenochrome (Hoffer 1957a). The raised level of activity of the sympathetic ganglia (which are cholinergic) thereby occasioned will lead to an increased output of adrenaline and so of the toxins which may be responsible for schizophrenia

A further advantage of the theory that metabolic products of adrenaline are responsible for schizophrenia is that it enables us to explain quite simply the role of psychological factors in schizophrenia One may postulate two factors (1) a genetic predisposition which may be stronger in some people than others, and (2) different patterns of emotional experience that, lasting for a sufficient time, may give rise to different patterns of biochemical activity in the vastly complex and variegated anatomical and biochemical mechanisms that underlie the experience, coordination, and expression of emotions, attitudes, dreams, wishes, unconscious desires, &c Some of these patterns may be more susceptible than others to the action of the toxins which produce schizophrenia Some may even produce such toxins or function at a degree of neurohumoral imbalance in the mechanisms sufficient to cause aberrant behaviour typical of schizophrenia One should not underestimate the biochemical and electrical storms that must sweep through the brain in the advent of powerful emotions The extreme range of symptoms and the variety of individual responses to L S D and mescaline again suggest that there are great individual biochemical differences in the higher mental functions

A final advantage of our hypothesis is that there are already well-known metabolic diseases due to abnormalities in the metabolism of tyrosine (adrenaline is a derivative of tyrosine) phenylpyruvic oligophrenia, alkaptonuria, albinism, and tyrosinosis

In view of all this evidence it is safe to conclude that there are now enough facts to show that purely psychogenic theories of the causation of schizophrenia along psychodynamic lines can no longer be held as total explanations of the causation of schizophrenia Their place should be in a presentation of contributory factors, as indeed are the biochemical factors I have been discussing

I am most grateful to Dr Julius Axelrod, Dr Erminio Costa, Dr Aaron Feldstein, Dr Harold E Himwich, Dr Hudson Hoagland, Dr Abram Hoffer, Dr Sten Martens, and Dr Humphrey Osmond for their help and welcome advice

REFERENCES

Abood, L G , Gibbs, F A , Gibbs, E (1957) *Arch Neurol Psychiat , Chicago*, 77, 643
— Romanchek, L (1957) *Ann N Y Acad Sci* 66, 812
Ashby, W R (1950) *Amer J Psychiat* 106, 48
Axelrod, J (1957) *Science*, 126, 400
— (1958) *Amer J Psychiat* (in the press)
— Brady, R. O , Witkop, B , Evarts, E B (1957) *Ann N Y Acad Sci* 66, 435
Birkhauser, H (1941) *Schweiz med Wschr* 71, 750
Bogdanski D F , Weissbach, H , Udenfriend, S (1957) *J Neurochem* 1, 272
Brodie, B B , Shore, P A (1957) *Ann N Y Acad Sci* 66, 631
Buscaino, V M (1952) *Int Congr Neuropath* 545
Carlsson, A , Lindqvist, M , Magnusson, T (1957) *Nature, Lond* 180, 1200
Costa, E (1956) *Proc Soc exp Biol , N Y* 91, 39
— Aprison, M H. (1958) *J nerv ment Dis* 126, 289
— Rinaldi, F (1958) *Amer J Physiol* (in the press)
Ehrenthell, O F (1957) *Arch Neurol Psychiat , Chicago*, 77, 178
Fedoroff, S , Hoffer, A (1956) *J nerv ment Dis* 124, 396
Finkelman, I , Stephens, W M (1936) *J Neurol Psychopath* 16, 321
Fischer R. (1953) *Science*, 118, 409
Gastaldi, G , De Renzi, E , Manzini, B , Franceschini, J (1957) *Int Congr Psychiat*
Harley-Mason, J , Laird, A , Smythies, J R. (1957) *Confinr neurol , Basel* (in the press)
Heacock, R. A , Nerenberg, C., Payza, A N (1958) *Canad J Chem* 36, 853
Heath, R G , Leach, B E., Byers, L W , Martens, S , Feigley, C A (1958) *Amer J Psychiat* 114, 683
Hoagland, H (1957) *Ann N Y Acad Sci* 66, 445
Hoffer, A (1957a) *J clin exp Psychopath* 18, 27
— (1957b) *in* Hormones, Brain Function and Behaviour (edited by H Hoagland) New York
— Kenyon, M (1957) *Arch Neurol Psychiat , Chicago*, 77, 437
— Osmond, H (1958) (in the press)
— — Smythies, J (1954) *J ment Sci* 100, 29
Holland, B , Cohen, G , Goldenberg, M , Sha, J , Leifer, L (1958) *Fed Proc* 17, 378
Kallmann, F J (1953) Heredity in Health and Mental Disorders New York.
Koch, W , Mann, S A. (1909) *Arch Neurol Psychiat , Lond* 4, 174
Lea, A J (1955) *J ment Sci* 101, 538
Leach, B E , Heath, R G (1956) *Arch Neurol Psychiat , Chicago*, 76, 444
Lovett Doust, J (1955) *J nerv ment Dis* 121, 516
Lucy, J D (1954) *ibid* 71, 619
McGeer, P L , McGeer, E G , Gibson, W C (1956) *Science*, 123, 1029
Mann, P J G , Quastel, J H (1940) *Biochem J* 34, 414
Meyerhof, O , Randall, L O (1948) *Arch Biochem* 17, 171
Öström A (1951) *ibid* 33, 484
— Skang, O (1950) *Acta psychiat , Kbh* 25, 437
Osmond, H (1957) *Ann N Y Acad Sci* 66, 418
— Smythies, J (1952) *J ment Sci* 98, 309
Ostfeld, A M , Abood, L G , Marcus, D A (1958) *Arch Neurol Psychiat , Chicago*, 79, 317
Patzig, B , Block, W (1953) *Naturwissenschaften*, 40, 13
Pfeiffer, C C , Jenney, E H (1957) *Ann N Y Acad Sci* 66, 753
— — Gallagher, W , Smith, R. P , Bevan, W , Jr , Killam, K F , Killam, E K , Blackmore, W (1957) *Science*, 126, 610
Pfister, H O (1938) *Amer J Psychiat* 94, 109
Reider, H P (1957) *Psychiat Neurol* 134, 378
Resnick, O , Wolfe, J , Freeman, H , Elmadjian, F (1958) *Fed Proc* 17, 131
Richter, D (1957) *in* Schizophrenia London and New York
Riegelhaupt, L M (1956) *J nerv ment Dis* 123, 383
Rinkel, M , Hyde, R W , Solomon, H C (1954) *Dis nerv Syst* 15, 259
Sands, D E (1957) *in* Schizophrenia (edited by D Richter) London and New York
Schwarz, B E , Wakim, K G , Bickford, R G , Lichtenheld, F R (1956) *Arch Neurol Psychiat , Chicago*, 75, 83
Shattock, F M (1950) *J ment Sci* 96, 32
Sherlock, S , Summerskill, W H J , White, L P , Phear, E A (1954) *Lancet*, ii, 454
Shore, P A , Mead, J A R., Kuntzman, R G , Spector, S , Brodie, B B (1957a) *Science*, 126, 1063
— Pletscher, A , Tomich, E G , Carlsson, A , Kuntzman, R , Brodie, B B (1957b) *Ann N Y Acad Sci* 66, 609
Stewart, F H (1930) *J ment Sci* 76, 277
Swartz, J , Semrad, E V (1951) *Psychosom Med* 13, 314
Trouton, D S (1958) *Science News*, 47, 31
Udenfriend, S , Bogdanski, D F , Weissbach, H (1956) *Fed Proc* 15, 493
Walaszek, E J , Smith, C M , Minz B (1958) *ibid* 17, 416
Witt, P N (1954) *Helv physiol acta*, 12, 327
Woolley, D W , Shaw, E (1954) *Science*, 119, 587
Zeller, E A. (1958) *J clin exp Psychopath* 19, 106

Congress

DIABETES

The third congress of the International Diabetes Federation was held in Dusseldorf from July 21 to 25, under the joint presidency of Prof. J P Hoet (Louvain) and Prof K Oberdisse (Dusseldorf) The congress received a telegram of welcome from Dr Adenauer, and honorary degrees were awarded to Dr E P Joslin and (in his absence) to Prof B A Houssay

In his Banting memorial lecture Prof G Katsch (Greifswald) spoke on Conditions for Conditioned Health He gave a comprehensive review of the social aspects of diabetes and repeated the advice to diabetics which is inscribed on the walls of his own clinic—"courage, moderation, and activity"

The congress sessions were divided into lay and scientific, and usually one lay and two scientific sessions were in progress simultaneously Virtually every aspect of diabetes was discussed, most time being devoted to the oral antidiabetic compounds, largely exploited since the Cambridge congress three years ago, and to various aspects of diabetic angiopathy, which is a problem of growing importance

Action of Insulin

The discussion of the action of insulin left the subject more open than it had been three years previously There is now no agreement about the importance or otherwise of insulin's action on the liver, especially in view of the negative results of Ashmore, Cahill, Earle, and Zottu on the effect of insulin on glucose production by the liver measured directly in experimental animals

Prof C de Duve (Louvain) still believed, however, that insulin affected hepatic gluconeogenesis primarily and not secondarily The evidence for the permeability hypothesis of insulin's action was well stated by Dr R Levine (Chicago) and Dr C R Park (Nashville) Dr Park believed that glucose permeates the cell by an enzymic process, and Dr B L Horecker (Paris) drew some interesting analogies with enzymic blocks of sugar permeases in mutants of *Escherichia coli* Dr P J Randle (Cambridge) suggested that insulin permits glucose to enter the cell by inhibiting the role of energy-rich phosphate bonds in establishing the barrier to glucose on the cell surface Anoxia or salicylates seem to encourage the permeation of glucose by a direct inhibition of oxidative phosphorylation

Dr D B Martin (Boston) described the immediate direct action of insulin on adipose tissue in contrast to the apparently delayed effect of insulin on liver Prof C N H Long (New Haven) indicated that the effects of the adrenal glucocorticoids on the liver were independent of insulin, and referred to steroid diabetes as an overflow diabetes, the excess glucose coming from increased gluconeogenesis in the liver and a partial block of glucose utilisation in the muscles

Insulin Assay

Some of the reasons were discussed for the different serum values obtained by slightly differing techniques based on the isolated rat diaphragm Dr H v d Geld (Amsterdam) considered that small amounts of adrenaline significantly opposed the action of insulin by reducing glucose uptake by the diaphragm, and there was general agreement that higher absolute values of insulin activity were obtained if dilute rather than whole serum was used It was suggested that results of different workers would be more comparable if a 1-in-10 dilution of serum was used, and that the results should be expressed as units of insulin activity per litre of serum

Dr Martin described the advantages of the insulin assay using rat adipose tissue and ^{14}C glucose The sensitivity of the method is similar to that employing rat diaphragm, as described by Dr J Vallance-Owen (London) and Dr P H Wright (London) Insulin activity can be shown to be associated with the serum-proteins, mainly the β-globulins according to the Amsterdam group, or the electrophoretically slow-moving albumin according to Dr K W Taylor and Dr Randle (Cambridge)

Various insulin inhibitors have been recognised in serum These include insulin antibodies in the inter-γ-β-globulin zone, the lipoproteins in alloxan-diabetic rats, and fractions in the serum of depancreatised cats, dependent on intact adrenal and pituitary glands, as were described by Dr R H Williams (Seattle) Dr J B Field (Bethesda) has found an additional insulin antagonist, migrating electrophoretically with the α_1 globulins of patients in diabetic ketosis Dr W Oakley (London) described the dramatic effect of prednisone in reducing insulin resistance in certain types of diabetes, which he has been studying

Diabetic Angiopathy

Dr D Adlersberg (New York) emphasised the ætiological role of raised serum-triglyceride levels, and Prof P A Bastenie (Brussels) drew attention to the high rate of excretion of adrenal 11-oxysteroids in such patients Prof M Burger (Leipzig) considered that insulin lack directly affected the capillaries and thus the blood-pressure and eventually the electrocardiographic findings Dr H T Ricketts (Chicago) hoped to exclude genetic factors by working with dogs with experimental diabetes of long duration The role of poor diabetic control in promoting angiopathy was clear but less important than simple ageing Prof K Lundbaek (Aarhus) described the long-term development of diabetic vascular disease in the human, and suggested that it was the cause of other late complications, such as rubeosis iridis diabetica, diabetic osteopathy, the " stiff hands syndrome ", and multiple areolar exudates of the retina Little helpful information regarding the treatment of angiopathy was forthcoming apart from the desirability of good diabetic control

Discussing diabetic nephropathy, Dr H F Root (Boston) emphasised its increasing importance as a cause of death in early-onset diabetics, but he believed that optimal control could postpone or prevent its development Dr J F Hartmann (Minneapolis), on the other hand, using electron microscopy of renal biopsies, had found evidence of renal involvement as early as five months from the clinical onset of diabetes Dr A Goth (Budapest) produced renal lesions in rats by causing wide variations in the blood-sugar with insulin alternating with glucose by stomach tube Prof P Kimmelstiel (Milwaukee) showed a series of beautiful slides illustrating the diabetic kidney condition named after himself and Prof Clifford Wilson (London) The stages of diabetic retinopathy were also well illustrated by Dr R Thiel (Frankfurt) Dr T Yoshida (Osaka) claimed that calcium pantothenate in association with good diabetic control effectively relieved the symptoms of diabetic neuropathy

Intermediary Metabolism in Diabetes

Dr O Wieland (Munich) drew attention to the probable competition between the metabolites of fat and carbohydrate for the available coenzyme A, which was concerned with acetylation processes Dr I Kelsey Fry (London) had studied the changes in blood-pyruvate levels during glucose and glucose and insulin loads in normal subjects and diabetics Only " brittle " diabetics showed a consistent pattern with high fasting pyruvate levels, unaffected by glucose but increasing sharply after insulin and glucose He suggested that diabetics had a metabolic block at the level of pyruvic-acid-oxidase, and integrated this suggestion with the effect of dimercaprol (BAL) in reducing blood-pyruvate and glucose levels in such diabetics

Diabetes and Pregnancy

Dr A Hagen (Gentofte, Denmark) performed a useful service in establishing the blood-sugar values of normal and prediabetic women during pregnancy Dr J J Hoet described experience in his father's clinic in Louvain, which specialises in the study of prediabetic pathological pregnancies Dr Hoet indicated his faith in the beneficial effect of insulin, even in prediabetic pregnancies, and of thyroid when indicated The infant mortality of diabetic pregnancies can be most effectively reduced by strict diabeic control, as was illustrated by the findings of Dr J M Malins (Birmingham) With improved survival-rates the incidence of congenital anomalies in the babies would assume increasing importance, and Dr R G Paley (Leeds) reported studies on this aspect

Dr M Osler (Copenhagen) measured the total body-water and extracellular water in the newborn infants of normal and of diabetic mothers The infants of diabetic mothers contained significantly less water, presumably because their body contained relatively more fat and glycogen than that of infants of normal mothers Dr R Boulin (Paris) made the interesting point that diabetic mothers have nearly three times the tendency of diabetic fathers to hand down the diabetes to their children

Oral Antidiabetic Drugs

Much of the discussion of the oral antidiabetic compounds centred on the mechanism of the hypoglycæmic action of the sulphonylureas Prof A Loubatières (Montpellier) felt confident that these compounds stimulated the release of insulin and later the hyperplasia of the β cells of the islets of Langerhans, but his work was based on experimental animals, not man Investigators of human diabetes, such as Dr T Munkner (Copenhagen), had shown that tolbutamide reduced the hepatic glucose output without changing the hepatic or limb blood-flow or affecting the arteriovenous blood-sugar difference in the leg Prof J D Achelis (Mannheim-Waldhof) agreed that some of the drug's action in humans is extra-pancreatic Prof C V Holt (Hamburg) attributed the main hypoglycæmic action in man to a stimulation of endogenous insulin secretion, and other investigators brought forward evidence to support this view Thus, Dr E F Pfeiffer (Boston) found a greater increase in the insulin activity of the portal venous blood of animals receiving sulphonylureas than that of the femoral venous blood This raised the question whether insulin in the portal venous circulation had a different effect from insulin in the systemic circulation Dr L L Madison (Dallas) had evidence to support this suggestion Thus in dogs the slow administration of insulin into the portal vein produced as much hypoglycæmia as a peripheral injection, but with much less effect on the arteriovenous blood-sugar differences Moreover, the hepatic binding of ^{131}I-labelled insulin was significantly greater when it was given into the portal vein than when it was injected systemically Prof W J H Butterfield (London) and Dr O J Rafaelson (Aarhus) confirmed that the sulphonylureas increased the uptake of glucose in the muscles of the intact human and of the isolated rat diaphragm respectively This could be explained by an insulin-like action, although it did not constitute a proof Further confirmation was provided by Prof Russell Fraser and his colleagues (London), for they found in a blind trial that tolbutamide would raise the plasma-insulin activity only in those diabetics who responded satisfactorily to the hypoglycæmic action of tolbutamide It would thus appear that the relatively great effect of the hypoglycæmic sulphonylureas on the liver as compared with on the muscles (Dr V Conard, Brussels) might be explicable if endogenous insulin was released and had its main effect on the liver

Many studies were reported of the comparative toxicity and efficacy of carbutamide, tolbutamide, and the new sulphonylurea, chlorpropamide European workers have not found cause to avoid carbutamide as studiously as their American colleagues, who were alarmed by early reports of bone-marrow depression Luckily the serious effects of tolbutamide on the liver of dogs have not been noted in man or indeed in other experimental animals There has been an increasing tendency to use carbutamide only in small doses (Dr R Boulin, Paris) or in intermittent courses (Dr I Murray, Glasgow) The toxicity of tolbutamide was less than that of carbutamide (Dr F Bertram, Hamburg, Dr A Marble, Boston), but neither compound was as potent a hypoglycæmic agent as chlorpropamide, which needed to be given in a dose of only 200–500 mg per day to maintain its effect The long-term toxicity of chlorpropamide has still to be established, but it is already apparent that doses comparable to those used for tolbutamide are certainly toxic (Prof H A Heinson, Zeven, Dr Joan Walker, Leicester)

Much information was also presented about the hypoglycæmic effect and toxicity of another oral antidiabetic compound, phenylethylbiguanide (D B I) and its analogues Such compounds inhibit certain oxidative enzymes (Dr R H WILLIAMS, Seattle) and increase the glucose uptake even of depancreatised animals or of juvenile diabetics Hepatic gluconeogenesis is sharply depressed, and doses of more than 100–200 mg per day produce a high incidence of toxic effects, such as anorexia, nausea, vomiting, diarrhœa, weakness, or a metallic taste in the mouth Dr P WHITE (Boston) has shown that D B I can reduce the insulin requirement of juvenile diabetics and be used alone in a few of them Such synergism between different hypoglycæmic agents was illustrated in a case of insulin-resistant diabetes by Dr N BILHAN (Istanbul), using tolbutamide with insulin, and by the use of salicylates with sulphonylureas by Dr J M STOWERS (Dundee)

A New Insulin

Dr J SCHLICHTKRULL, of the Novo Laboratories, Copenhagen, described a new insulin, which may be an improvement on the lente series No zinc is added to the insulin crystals, and a quicker initial action than that of lente insulin is obtained by including a proportion of pig insulin in a mixture with slower acting beef insulin, prepared in the same way

Detection of Diabetes

The lay sessions of the congress made progress in establishing the need for and methods of diabetes detection drives A committee representing 14 countries was formed and hopes to work in association with the World Health Organisation Dr M NAKAYAMA's detection drive among people over 40 years of age in Tokyo revealed 3·1% of previously unknown diabetics and another 3·3% of suspected diabetics Dr J J A REID (Dundee) discussed the results of his personal survey of employment problems among diabetics, and Mr J G L JACKSON (London) reported on the results of a questionnaire about employment sent to the 22,000 members of the British Diabetic Association The expense of diabetic diets and insulin is still a problem in many parts of the world. Dr W. TROUP (Ottawa) described the increasingly progressive attitude of insurance companies to the life assurance of diabetics

Parliament

Commemoration Day

WHEN the National Health Service was started ten years ago Mr ANEURIN BEVAN was Minister of Health, and on July 30 he appropriately opened the debate held in the House of Commons to mark its tenth anniversary Behind the service, he said, lay two principles—the provision of a comprehensive, free, health service for all the people of the country in time of need, and the redistribution of the national income by a special method of financing the service On the whole he thought that the first principle had been achieved and that there was general, though not uncritical, satisfaction with the therapeutic side of the service

About the financial side he confessed that he was getting a little worried When the service was being planned, he had rejected the method of insurance as inapplicable to a scheme of this kind and had decided that the fairest way to finance the service was from Exchequer funds by general taxation As the Treasury was to carry the full cost of the service, it claimed the portion of the National Health Insurance contribution which had formerly been used for medical benefits This was reasonable enough, but, Mr Bevan stressed, it was an appropriation-in-aid taken from the Insurance Fund by the Treasury, and there was no organic, financial, or administrative link between National Insurance and the National Health Service By assuming this link, the Government, instead of increasing taxation to find additional money for the service, had called for the money from the National Insurance Fund by a poll tax This was an unjustified transfer of the burden from the well-to-do to the poorest

One of the difficulties of the service had been the number of Ministers They had followed one after the other, to their mutual embarrassment and to the dismay of the nation By the time that they had acquired a jealousy for their position and a knowledge of it, they were sent away They had not enough time in office to acquire sufficient stature to be able to stand against the importunities of the Treasury

Mr Bevan had always regarded pay-beds as one of the concessions which had to be made to the pressures of the moment when the service was started He was distressed to learn that this concession was sometimes abused. He would not say for a single moment that the practice of allowing a paying patient to jump the hospital waiting-list was universal, but it had amounted to so grave an abuse as to impair the service

When people talked about the cost of the service he hoped that they would take into account that the service had a secret silent column which never appeared in the balance sheet It comprised the enormous number of people who were back at work and who would not be there without its help

Mr DEREK WALKER-SMITH, the Minister of Health, thought that ten years had been long enough to establish some sound record of performance, but was yet short enough to make it appropriate to concentrate on the future rather than the past Two signposts for future action were, he suggested, provided by our success with tuberculosis and diphtheria It showed the importance and potential of preventive medicine and the possibility of solving the accommodation problem of our hospitals by eliminating some diseases Two of our gravest problems—the care of the aged and of the mentally ill—had a common denominator In both we sought a shift of emphasis to outpatient treatment and care within the community Only in this way could we hope to have a service adequate to the needs of the patients without creating a burden too great for our resources to bear

But whatever success we achieved in this policy, there would always be an important residue of patients who would need care in hospital At present the running cost of hospitals took nearly 54% of our total expenditure on the health service Where so much money was being spent we must seek the highest common factor of efficiency and economy in administration The Ministry's experimental organisation and methods service had already shown that we could best ensure economy by critical and detailed analysis of hospital work on the spot Particularly in manual work large savings of time could sometimes be made, and these potential savings were a hidden reserve which could be used to offset the recent reduction in working hours and to relieve our nurses of extraneous tasks The present experimental O and M unit was to be enlarged and made permanent under a full-time assistant secretary by the Ministry He was also considering a suggestion by the Royal College of Nursing that an advisory council on work study should be set up

The country had made a very considerable investment in health, and he thought that with the years we should see an increasing return The return we needed was not only better treatment and improved prospects of cure, but the prevention and where possible the elimination of disease, resulting in a positive improvement in health which would be reflected "in the factory, the foundry, and the farm, and not merely in the convalescent home"

Dr A. D D BROUGHTON believed that one of the most serious problems of the service was the overcrowding in the mental hospitals, yet he asked the Minister to resist proposals to build new hospitals to relieve congestion. Dr Broughton was sure that wherever possible the patients should remain in familiar surroundings and if possible at work.

Mr ROBERT COOKE thought that the craving for new apparatus should also be resisted. These things quickly went out of date and this could lead to work Clearly the best facilities should be available, but not necessarily in every hospital

Sir FREDERICK MESSER believed that more money should be spent on keeping patients out of hospital He would like to see the executive committee become a more effective administrative unit, with closer liaison between general practitioners and the local health authority, the domiciliary services could usefully be extended One of the inconsistencies of the N H S was that a patient usually had to pay for a home help, yet he was not asked for any contribution towards the wages of the wardmaid Stronger incentives for a more efficient domiciliary service would, in his view, be better for the patient and cheaper for the taxpayer

Mr Kenneth Robinson was disturbed by the steady drift from whole-time to part-time consultants He, too, thought that some part-time consultants were abusing the pay-bed facilities of the hospital But the main thing about consultants was that we had not nearly enough of them In some areas and in some specialties we needed many more All over the country senior registrars and even registrars were doing work which should be done by consultants What was even more disturbing was that the quality of the registrars coming forward was beginning to deteriorate The worry and frustration among registrars had acted as a powerful disincentive to medical graduates to make their way on to the consultants' ladder

Mr Arthur Blenkinsop was dismayed by the calm assumption that we were wasting enormous sums on the service when in fact the total expenditure was by no means so terrifyingly great in real terms People were terrified because for the first time they were seeing the total expenditure on medical care expressed in money Our expenditure per head by the population was no greater than that of other countries, and much less than that of the United States He regretted a lack of leadership in the Ministry and among the professions concerned with the service As a result, a great deal of the time of highly intelligent and well-trained people was spent on all kinds of professional squabbles which would not be necessary if there were a greater sense of what kind of service we were trying to build and what were the main problems we were trying to solve For instance, we did not seem to appreciate the urgency and importance of industrial health It should be the natural job of practitioners working in groups and linked with industry, as at Harlow and Slough Again, the present local-authority services were very haphazard, yet if we were to cope with an ageing population, they should be given priority Yet by introducing the block-grant procedure, the Government would make it much more difficult for the local authorities to expand their health services What, for instance, was the good of decertifying patients if the local authorities were unable to provide residential accommodation for them?

Mr John Cronin, f r c s, said that though the profession had cooperated in the N H S in an able and honourable way, few doctors had any idea of the economics of the service, and none of them by its administrative framework had any incentive towards reasonable economy even in the best interest of the patient He believed that the service would gain from a mild and general economic supervision of doctors, as doctors, by doctors

Dr Edith Summerskill also thought that the Minister should reconsider fundamentals, and suggested that the capitation system was not calculated to improve the quality of the service For some people it only served as an incentive to achieve the maximum list of patients and encouraged acquiescent prescribing Again was it economical for us to have part-time rather than whole-time consultants? The payment of a consultant by sessions might encourage him to keep his outpatient department fully occupied and his beds full

Mr Richard Thompson, parliamentary secretary to the Ministry, agreed that the local-authority community care services should be enlarged The Government had made it clear that they did not consider that the introduction of the general grant would hinder this The local authorities' associations had, however, suggested that it would be preferable that special financial provision should be made for these services and their views were being very carefully considered

Turning to the future he said that our general aim must clearly be to keep those not in actual need of hospital care and treatment out of hospital and in the community for as long as possible Of all our public services the N H S probably depended most on voluntary help for its administration, and we must be grateful to the members of hospital boards and committees for their work in this worthwhile project "It is in this spirit of cooperation and dedication to a great cause that we can face the future with confidence"

Artificial Insemination

The Earl of Feversham has agreed to serve as chairman of the proposed departmental committee on artificial insemination The committee's terms of reference are

> To inquire into the existing practice of human artificial insemination and its legal consequences and to consider whether, taking account of the interests of individuals involved and of society as a whole, any change in the law is necessary or desirable

Royal Assent

Bills which received the Royal Assent before the end of the session included the Medical Act, 1956 (Amendment) Bill and the Children Bill

QUESTION TIME

Charing Cross Hospital

Mr A G F Rippon asked the Minister of Health whether he had reached a decision regarding the future of Charing Cross Hospital —Mr Derek Walker-Smith replied On Feb 9, 1955, the House was informed by the then Minister that the Government's plans for hospital building expected to start in the next few years included a project for the rebuilding of Charing Cross Hospital at Northwick Park, Harrow This proposal has had to be abandoned because further consideration by the University of London and the University Grants Committee caused these bodies to decide that it was not in the best interests of medical education to remove the Charing Cross Hospital Medical School to Northwick Park

The existing Charing Cross Hospital building is outmoded and inadequate for hospital purposes, and it cannot be properly redeveloped on the same site To meet University requirements, the new site must be within reasonable access of all the facilities of the University, including the basic sciences and general student activities, and in August last the responsible hospital authorities were asked to consider the possibility of rebuilding on the site of the existing Fulham Hospital, which is in close proximity to these University facilities and which also requires rebuilding I am glad to say that a large measure of agreement has been reached by the responsible hospital authorities about the practicability of amalgamating Charing Cross Hospital, the West London Hospital, the Fulham Hospital, and the Fulham Maternity Hospital, as a first step towards the ultimate replacement of all of them by a new general teaching hospital at Fulham

I have given close and careful consideration to all the representations made to me, including those made by the committee headed by the Mayor of Fulham, and I am satisfied that the Board of Governors of Charing Cross Hospital, in close cooperation with the South West Metropolitan Regional Hospital Board, will provide a service to the locality which will compare favourably with that which might have been provided by the rebuilding of Fulham Hospital as a non-teaching hospital

I propose, therefore, to make arrangements for the proposed regrouping at the earliest practicable date so that the replanning of the new teaching hospital may proceed without delay The necessary facilities for clinical teaching will be provided at the new hospital, but the question of preclinical facilities is under consideration in consultation with the University and the University Grants Committee

Institute of Criminology

Mr H M Hyde asked the Home Secretary to make a statement on the official proposal for an institute of criminology

Mr R A Butler replied Discussions have been proceeding with university authorities and I am also consulting the University Grants Committee. I have now been informed by the Vice-Chancellor of Cambridge University that, provided the necessary funds can be made available, the university will be glad to consider the establishment of an institute of criminology, whose functions would include both teaching and research, as well as facilities for exchange of views and information with those concerned with the practical administration of the law. The nucleus of the institute would be the existing department of criminal science, but it would be developed on a broader basis and steps would be taken to associate all interested faculties with its management. I have told the Vice-Chancellor that I warmly welcome this proposal and that I am confident that its fulfilment would make an indispensable contribution to the study of the problems of crime and the treatment of offenders.

Family Planning

Mrs LENA JEGER asked the Minister what were the present facilities within the National Health Service for family planning advice and treatment, and why he did not propose to encourage a widening of existing facilities.—Mr WALKER-SMITH replied: The present facilities are for advice and treatment where pregnancy would be detrimental to health. Help is also given in some areas to voluntary associations by making premises available. I do not consider that there is a sufficient case in present circumstances for seeking to widen these facilities.

New Hospitals

Since 1948, under the National Health Service in Great Britain 1 new hospital has been completed, 3 others are in part use, and 8 are under construction.

Public Health

Sickness Benefit

THE biggest influenza epidemic since the National Insurance scheme began brought new claims for sickness benefit in 1957 up to the record figure of 9½ million. According to the report of the Ministry of Pensions and National Insurance for 1957 which has just been published,[1] 5 million claims (twice the average for the season) were received between late August and the end of the year, suggesting that 1 in 8 of the 20 million people insured for sickness benefit may have had influenza. The peak was reached in the first week of October, when 567,000 claims came in—130,000 more than the highest week's figure in the epidemic of 1951. The epidemic is estimated to have cost the National Insurance Fund £10 million.

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[1] Cmd 493. H.M. Stationery Office. 8s.

Infectious Diseases in England and Wales

Disease	Week ended July			
	5	12	19	26*
Diphtheria	3		3	
Dysentery	919	741	712	637
Encephalitis				
Infective	4	4	1	5
Post-infectious	2	1	5	8
Food-poisoning	342	228	332	486
Measles, excluding rubella	6442	7078	6674	6594
Meningococcal infection	21	15	15	16
Ophthalmia neonatorum	17	12	23	15
Paratyphoid fever	4	4	4	11
Pneumonia, primary or influenzal	232	220	220	182
Poliomyelitis				
Paralytic	30	35	37	38
Non-paralytic	18	24	20	25
Puerperal pyrexia	183	229	223	188
Scarlet fever	665	625	651	672
Smallpox				
Tuberculosis				
Respiratory	535	497	578	521
Meninges and C.N.S.	4	12	8	6
Other	56	58	73	67
Typhoid fever	1	18	4	
Whooping-cough	882	816	827	749

* Not including late returns

Special Articles

Medical Staffing of Hospitals

THE Joint Working Party on Medical Staffing of Hospitals has elected Prof. Robert Platt, P.R.C.P., as its chairman.

This working party was appointed by the Minister of Health, the Secretary of State for Scotland, and the Joint Consultants Committee to study, in the light of experience of the hospital service since 1948 and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organised.

The working party is inviting regional hospital boards, professional organisations including organisations of specialists and the associations of hospital authorities, to submit statements of evidence. Any other body or person desiring to submit evidence should notify one of the joint secretaries before the end of October. The joint secretaries are Mr N. C. Rowland of the Ministry of Health and Dr D. P. Stevenson of the British Medical Association.

Medicine and the Law

Duty to Disclose Epilepsy

A PERSON who suffers from epileptic fits is not under any general duty to disclose the fact, but the law recognises that there are circumstances in which he ought to do so.

A few years ago a workman took employment as a painter without informing his employers that he was subject to epileptic fits and had been warned by his doctor not to work at heights. While working on a platform about 20 feet above ground he had a fit, fell to the ground, and was killed. The platform did not conform to statutory regulations and had it been properly protected the man might not have fallen to the ground. The court held that the two parties were equally at fault, with the result that the damages payable to the widow by the employers were reduced by half.[1]

Even more compelling is the duty of an epileptic who is contemplating marriage. Failure to disclose the facts to the intended spouse may later result in the marriage being nullified. A decree of nullity under section 8 of the Matrimonial Causes Act, 1950, has been granted to a woman who married in ignorance of the fact that her husband suffered from epileptic fits.[2] At the time of the wedding the man was 21, the bride 18. The man had the first attack three months before the wedding when discussing the arrangements with her. He did not have hospital treatment as his doctor, who diagnosed an epileptic fit, advised. He had a similar attack on the occasion of the wedding ceremony before the bride had got to the church; she was not informed of it although the ceremony was late.

Although the man had lodged at the home of the girl's parents before the wedding, the judge was satisfied that she was entirely ignorant of his condition until after she left him.

Section 8 of the Matrimonial Causes Act, 1950, provides that recurrent attacks of epilepsy are sufficient ground for a decree of nullity provided three conditions are satisfied. The petitioner must be ignorant of the fact at the time of the marriage, proceedings must be instituted within a year of the marriage, and marital intercourse must not have taken place with the petitioner's consent after discovery of the fact.

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[1] Cork v. Kirby Maclean (1952).

[2] *Daily Telegraph*, July 23, 1958.

In England Now

A Running Commentary by Peripatetic Correspondents

NOT being an efficient G P —that is, not having a secretary—I'm constantly facing the problem of remembering my patients' names When one enters my surgery I often find myself saying (to myself, of course) "Ah! here comes 193-Copthorne-Avenue, or 61-Huntscliff-Common" Then aloud, diffidently and apologetically—"Er, I'm afraid I've forgotten your name"

Not so with the Brown family I know them all very well Mr Brown, now resting in peace, I saw every month for all the eight years I had been in practice He needed dressings for his eczema Then I saw him almost daily for many many weeks while he was under my care in the local G P hospital and during his final long illness at home Mrs Brown, too, I have greeted many times during my repeated cures of her leg ulcers—the relapses, that is Then there's Mr Brown's sister, who had a very severe ophthalmic herpes, and there's unmarried daughter Joan—I Q not very high and definitely odd The son, Eddie, has 37 attendances recorded during the past eight years, strangely enough without there ever having been noted a firm diagnosis (should it be inadequate personality or perhaps *inadequate family doctor*?) So when a Brown comes into my surgery I don't say to myself, "Ah! here comes 34-Acacia-Drive," I say "Here's Eddie Brown" or "Here's Joan Brown"

But I hadn't seen any of the family for three or four weeks, when a note came through my door "Would you please come to see Mrs Brown She has been at M—— for a few days and has had a stroke She will be home at 5 o'clock" At 5 15 sharp I am at 34, Acacia Drive "Hello, Mrs Brown, what's happened?" I asked "Didn't the doctor at M—— telephone you?" she said "No," I replied, "not yet" "Well," said Mrs Brown, "I expect he's had some difficulty in finding your number None of us could remember your name"

* * *

The heart bleeds for your correspondent of last week beneath whom plastic seats are continually crumbling Such a long tale of disintegration must surely have a cause and he had better take a careful look at his profile in a full-length mirror, or better still ask for the candid comments of his wife who will be more objective There comes a time when the odd stones come on us with a rush 13¹/₂ is easily confused with 14¹/₂, and pretty soon it will be 15¹/₂, but by then the earlier figures have been forgotten and one goes about in the fond fiction that it was 15¹/₂ all along This is known as "repression of an intolerable memory" (Freud) and operates also on paunches, chins, bags under the eyes, and receding hair one cannot recall the time when these things weren't It also explains why old photograph albums get so easily misplaced

Insight comes slowly, and it is always easier to spot increasing disproportion in others realisation came ultimately to me, not through shattered seats, but tennis My service matured with increasing years and gained in power and reliability, as did my ground strokes middle-aged guile enhanced my skill and things were pretty good until I attempted the overhead smash Lobs which I used to "jump to" and catch squarely in the middle of the racket started to get lost in the short strings at the end, and this year hit the wood Next year I shall miss altogether It could be argued that people are lobbing higher these days, but I *know* It is all a question of power/weight ratio

* * *

I had no particular reason to question the mode of arrival and departure of the night sisters until one night after a party, when I happened to be on duty late, I came across a door which I had not noticed before I opened it and peeped in The room was bare except for a line of hooks on which hung in a neat row seven long cloaks, six were a dark green, the seventh was jet black On each cloak rested a high-pointed black cap, beside each cloak, propped against the wall, was a tall broom, on the ground beside each broom a huge black cat snoozed This sight aroused my suspicions

The next morning before dawn I hid myself near the front door hoping either to confirm or disprove my suspicions I hardly dared to breathe as the first sister appeared at the end of the corridor, came nearer, and walked past me She had changed out of uniform, wore a heavy overcoat, and carried a large bag I wondered what was in the bag She reached the front door, stood still for a second gazing about her, as though sensing that all was not quite as usual, opened the door and walked off down the drive Each sister left in turn, and last of all the night superintendent, whose bag was a size larger than the others, came into sight, and stood by the front door for a second before leaving I craned desperately from my hiding-place, and caught a glimpse of some jet-black cloth protruding from her bag This last effort, however, proved my undoing I fell forwards on my face in the middle of the corridor The night superintendent looked back "Good morning, doctor," she said I thought she said it rather spitefully I felt a little chastened, as she too departed down the drive

I suppose it is not for mortal eyes to see *exactly* how the night sisters come and go

* * *

Mrs X-Y was reluctant to send her baby to hospital However, I told her that her baby would be nursed by a specially picked staff in a special ward in a very good hospital and she gave her consent—influenced, I think, by the fact that I had had two babies myself

A few days later I went to the children's ward to see the baby and found her in the arms of a nurse who was trying to get her to sleep Apart from being very cross, my patient was doing well Sister was off duty, so the nurse and I walked up and down the ward for a time and I thought the baby was going to settle down But we happened to stop at the window and we discovered two buxom young women digging the hospital garden, and that seemed to make the baby crosser than ever The young lady gardeners were making a poor job of it and I was tempted to take the baby myself and send the nurse down to give them a hand He was a tough, muscular young fellow and would have finished the plot for them in no time, but I thought the head gardener might not like it So I left him rocking the baby, first on one arm and then on the other, and went on to report to Mrs X-Y I told her that it would have been difficult to find a better nurse

* * *

At lunch, the physicist was being sarcastic over clinicians using apparatus which they did not understand The only surgeon present rose at once to this bait and said that he would never dream of using anything which he did not thoroughly understand "Do you use diathermy?" asked the physicist "Of course," was the reply "Very well then, I will bet you sixpence that you cannot answer two out of four *elementary questions about it*" The surgeon looked rather shaken by this but had to agree These were the questions

(1) What type of current is used—e g, A C, D C, or interrupted? What is the approximate voltage and amperage?

(2) What happens when you switch over from "cutting" to "coagulating"?

(3) In what concentration of saline should the pad enclosing the indifferent electrode be soaked?

(4) How can a patient get burnt in areas remote from both the active and the indifferent electrode?

The surgeon's score was   no, my gallstone still bothers me and I think that he already suspects me of being a peripat

* * *

This year the Widdicombe Agricultural Show shows another loss The committee are thinking of including classes for doctors next year—e g

1 Doctors more than 6 feet
2 Doctors less than 6 feet
3 Working doctors
4 Doctors with student at foot
All entries to be properly qualified and on the Register

Letters to the Editor

REAPPEARANCE OF TABOPARESIS?

SIR,—Some senior and experienced psychiatrists have recently had cause to give considerable thought to the topic of taboparesis One British psychiatrist recently found that there was concern in responsible circles in America on the same topic. When the time-lag between primary infection with syphilis and the onset of taboparesis is considered, it appears possible that the recent virtual disappearance of taboparesis is due to the efficiency of arsenical treatment in the years before the large-scale employment of antibiotics

It may be that cases treated in the early years of the antibiotic era have yet to develop taboparesis The time factor suggests that the next few years may be particularly important in this respect Recently, a senior psychiatrist with considerable experience of neurosyphilis had four cases referred to him within a very short period—more cases than he had seen for a very long time previously Two of these cases could easily have been missed by a more junior man with little practical experience of taboparesis Moreover, some of the old characteristic physical signs seem to be changing somewhat

It may be hoped that fears of a reappearance of taboparesis on a considerable scale may prove groundless, but there appears to be reason for clinicians to be very alert on this topic, so that if an increase in the number of cases should occur, the sufferers from it may be diagnosed early and, therefore, successfully treated

The Royal Medico-Psychological Association, London, W 1

NOEL G HARRIS
Chairman
Public Relations Committee

CHILDREN IN HOSPITAL

SIR,—In a lecture given to the Central Council for Health Education, Professor Illingworth (July 26) has made some extraordinary statements about infectious-diseases hospitals Many of these provocative remarks were refuted at the conference but apparently with little effect on the subsequent publication of the lecture by the Council and by your journal

Professor Illingworth's personal experience of infectious-diseases hospitals would seem, from his lecture, to be limited to the pre-war era Only this can explain his recommendation that the great majority of cases of uncomplicated measles and scarlet fever should be nursed at home Of course, this has been the common practice for many years and certainly these cases are only rarely admitted to the infectious-diseases units in the London area

All would agree with his comment that children should not be admitted to infectious-diseases hospitals unless it is really necessary, a recommendation which would apply to children entering any hospital It is difficult to see, however, what advantage would be gained in establishing isolation units at each general and children's hospital except in sparsely populated areas The Royal College of Physicians view, that in every pædiatric unit isolation accommodation is essential, is a wise one, considering the frequency with which such units go into quarantine with chickenpox and measles, but to convert existing general and children's hospitals, so that infectious cases can be admitted as routine policy, would merely duplicate facilities already in existence. The arrogant assumption that only a pædiatrician is capable of looking after cases of gastroenteritis is shown in its true light when one considers the large number of such cases which have been efficiently treated by the medical and nursing staff of infectious-diseases units over many years Can it be that the pædiatric world, tiring of enuresis and metabolic rarities, is looking for fresh pastures?

The Professor's wildest assertion, "that a high proportion of children admitted to infectious-diseases hospitals are not suffering from an infectious disease at all", can only mean that he equates infectious disease with notifiable infectious disease, two entirely different matters Admittedly some forms of pneumonia and meningitis are not infectious, but the majority, including many of the viral and bacterial varieties, are most certainly so Can the infectivity of these conditions be determined at the time of admission? If it could, we would not be faced with the tragedy of paralytic poliomyelitis developing in a child admitted to a general children's ward for treatment of some other condition—an event not unknown in the experience of most physicians dealing with infectious diseases Yet the polio virus has low infectivity in comparison with the Echo virus, to mention only one No, Sir, cases of pneumonia and meningitis, in common with other infectious diseases, should continue to be admitted to isolation units for investigation and treatment, for only there can the interests of the individual and the safety of the community be reconciled

Coppetts Wood Hospital,
London, N 10

R T D EMOND
Physician-Superintendent.

SIR,—Professor Illingworth's lecture to the Central Council for Health Education contains some provocative assertions regarding infectious-disease hospitals His statement that "the great majority of cases of uncomplicated measles and scarlet fever should be nursed at home" comes about twenty years out of date and belongs not only to a pre-antibiotic era but to a pre-war era This has been the practice in Greater London, if not over most of the country, and has contributed to the great reduction in the number of available infectious-disease beds per thousand of the population over the past twenty years

Professor Illingworth states "The aim of cubicles is the prevention of cross-infection, and we all know how regrettably they fail to achieve this" Cross-infection is most likely to occur in *Escherichia coli* infective gastroenteritis and salmonella infections in infants Apart from these incidents cross-infection is no problem in infectious-disease hospitals where the cubicles are well planned and where the prevention of the spread of infection is instilled into all staff trained in these hospitals or units

His inaccurate assertion that only a pædiatrician has experience of infectious diseases requiring specialised treatment (e g, gastroenteritis) is quite out of place, bearing in mind the amount of good work that has been done throughout the years in infectious-disease hospitals Gastroenteritis, which he quotes, and of which we saw so much in the past, has now ceased to be the problem it was in this country

Could it be that, with the tremendous improvement in nutrition and in child health generally—partly contributed to by the public and school health services and education of parents, and partly by the advent of the antibiotic era—the pædiatric fraternity is looking for further spheres of activity, in which other people have worked when problems were greater than at present?

Neasden Hospital,
London, N W 10

W F TWINING McMATH

IDIOPATHIC THROMBOCYTOPENIC PURPURA AND DISSEMINATED LUPUS ERYTHEMATOSUS

SIR,—We were interested to read an annotation on the treatment of idiopathic thrombocytopenic purpura (I T P) in the *British Medical Journal* of July 20 which deals largely with two papers published by Dameshek and his colleagues[1,2] These authors claim that approximately 25% of all patients with apparently typical I T P in whom the spleen has been removed will eventually develop disseminated lupus erythematosus (D L E) This is contrary to our own experience, which is given in our paper in *The Lancet* of Aug 2 In none of the 42 cases of I T P submitted to splenectomy, and followed up for periods of from 1 to 29 years, did the clinical features of D L E develop This is also our experience in a large series of splenectomies carried out on patients with portal hypertension and hæmolytic anæmia We therefore consulted the two papers by Dameshek and his colleagues, and we find that, although the figure of 25% is given by these authors, they supply no details of the cases and no supporting evidence that splenectomy either caused D L E or hastened its onset

In the second paper an account of only 1 patient with "idiopathic" thrombocytopenic purpura is given A study of this case-record makes it clear that the patient had stiffness, limited movement, and spindling of the finger joints, and fever, coincidental with the onset of the thrombocytopenic purpura Accordingly it seems to us likely that a collagen disease was already in being This is admitted by the authors who state that " the possibility of a more fundamental disease such as D L E was considered" Whether the severe manifestations of D L E which developed 4 months after splenectomy were the result of the operation or were due to a spontaneous progression of the disease, can only be a matter of conjecture

Lastly, we agree with Dameshek and his colleagues that steroid therapy should be the first line of treatment both in acute and chronic I T P We do not agree, however, that splenectomy is potentially dangerous or of little therapeutic value, since none of our cases developed D L E, while 75% of our "short history" cases of I T P and 50% of our "long history" cases have remained well for periods which in some cases extend over 12 years

Edinburgh

STANLEY DAVIDSON
A I S MACPHERSON

ASPIRIN AND PEPTIC ULCER

SIR,—The possibility that aspirin may cause hæmorrhage is a matter of considerable importance to patients who have a chronic peptic ulcer, or the diathesis for acute gastric ulceration It is therefore unfortunate that Dr Allibone and Dr Flint (July 26) should "conclude that aspirin, although a gastric irritant, is a rare cause of hæmatemesis" when their data do not warrant such a conclusion Aspirin has been used so extensively and for so long that it cannot come as a surprise that 59 of their 129 controls took the drug, within two weeks of admission to hospital, without ill effect On the other hand, who can say how many of the 61 "series" patients who had taken aspirin precipitated their hæmorrhage (or perforation) by so doing? It is presumably among the ulcer group alone that the risk exists, and therefore a controlled investigation of this problem should be confined to such patients

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ROY M ACHESON

ULCERATIVE COLITIS

SIR,—In psychosomatic disorders there is to date a woeful lack of adequate research, and accordingly even the most tentative hypotheses have too readily gained the status of inviolable laws Dr Sim and Mr Brooke (July 19) are, therefore, to be congratulated on their attempt to test current psychosomatic hypotheses with respect to ulcerative colitis

Some methodological questions, however, arise For instance, do the members of the Ileostomy Association represent a fair cross-section of the ulcerative-colitis population? Further, the questionnaire method—as compared, for example, with the standard interview—may involve significant limitations The reader would have been further enlightened if the items of the questionnaire had been described in detail

Above all, a retrospective survey of the order of appearance of the symptoms of ulcerative colitis (which often arose many years previously) is, as the authors themselves concede, open to error Not only is heavy reliance thus placed upon the patients' memories but a distortion factor may be introduced if conflict-producing situations and emotional disturbance become subject after many years to repression and dissociation That this is liable to happen is indicated by Bastiaans and Groen,[1] who comment thus upon their study of psychological factors in ulcerative colitis patients "Usually the occurrence of such an event [i e, an acute emotional trauma within 48 hours before the illness began] was denied when the patients were asked outright, during the first interview, if anything had upset them When, however, they were given an opportunity to give their life history and encouraged to talk freely about their present situation they told of such events"

Dr Sim and Mr Brooke may have cast grave doubt upon certain hypotheses regarding ulcerative colitis, but this should not be mistaken for the death-knell of a psychosomatic approach to this disease Only long-term longitudinal studies of a prospective nature as well as careful experimental investigations, rather than cross-sectional studies, will permit a sober appraisal of possible emotional factors in this puzzling disease

Southern General Hospital,
Glasgow

A BALFOUR SCLARE

SIR,—Dr Sim and Mr Brooke (July 19) make a big sweep with a small broom when they conclude that the absence of diarrhœa as an initial symptom of ulcerative colitis leaves "little evidence to support existing psychosomatic hypotheses of the origin of the disease" For only in very specious and theoretical misapplication of Freudian theory can anyone so far turn their backs upon the disease in search of its causation

Respectable psychosomatic theories of ulcerative colitis must be based upon the known responses of the colon to emotion or the association of abnormal emotional constitution with the disease

The disturbances of colonic function most clearly induced by emotion have been (*a*) vascular and secretory changes in the mucosa, first described in dogs,[2] but repeatedly observed in man[3,4], and (*b*) changes in the tone and contractility of the colonic musculature Colonic spasm has been shown to be capable of producing rapid ulceration of the colonic mucosa in dogs[5]

The more durable of existing psychosomatic hypotheses are

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[1] Dameshek, W, Reeves, W H *Amer J med* 1956 21, 560

[2] Dameshek, W et al *J Amer med Ass* 1958 166, 1805

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[1] Bastiaans, J, Groen, J *in* Modern Trends in Psychosomatic Medicine, p 111 London, 1955

[2] Drury, A N, Florey, H, Florey, M E *J Physiol* 1929, 68, 173

[3] Almy, T P, Kern, F, Tulin, M *Gastroenterology* 1949, 12, 425

[4] Grace, W J, Wolf, S, Wolff, H G *J Amer med Ass* 1950, 142, 1044, *Gastroenterology*, 1950, 14, 93

[5] Lium, R, Porter, I E, *Arch intern Med* 1939, 63, 201

based upon well-observed facts In addition to emotionally induced changes in mucosa and muscle these include the many studies in emotional and personality types found in ulcerative colitis, from the pioneer clinical observations of Hurst [6] through the character studies of the thirties to the, in some cases, more detailed work of the past decade or so A few other studies not mentioned by Dr Sim and Mr Brooke are listed below [7-9]

The presence or absence of diarrhœa as an initial symptom does nothing whatever to detract from these many deep and massive studies of the psychogenesis of ulcerative colitis To all who have studied it carefully from both aspects this disease is so strikingly based upon a complex of body-mind relationship that it is distressing to find two modern writers who are willing to think such a frail criterion as the time of arrival of liquid stools can leave us "little evidence" of the deeply distorted characters and the profound physical and mental susceptibilities and sensitivities that are causally connected with the symptoms in sufferers from this disease

Dorrington Grove,
near Shrewsbury
RANYARD WEST

"EXPERIENCE AND INCENTIVE" AWARDS?

SIR,—The principle of differential payments to general practitioners for the *quality* as distinct from the *quantity* of their work appears at last to be receiving serious attention The stumbling-block of "merit" awards lies in the difficulty of finding a method to assess merit I do not believe that any system which depended primarily on the assessment of the merit of one practitioner by another practitioner could possibly succeed The idea that a board of consultants might do it would surely be as embarrassing to the consultants as it would be to the general practitioner

May I suggest therefore that the word "merit" be dropped altogether and that an alternative "experience and incentive" award be considered?

The difference in such an award is that it would not be beyond the reach of all G P s at some time in their careers For this reason I believe it would be more generally acceptable If payment for it was met out of some fund other than the central pool it could play a big part in what should be its *main* purpose—i e, the promotion of good general practice

For such an award only criteria that are fairly easily assessed could be used I would suggest

(1) 10 years' experience as a principal.
(2) A high standard of surgery premises and equipment.
(3) A list of patients not below a certain minimum, nor yet above a certain maximum considered locally suitable

To those critics of such yardsticks (e g, Burdon [10]) I would point out that while experience is no guarantee of merit, it is fair to assume that every doctor is a better doctor for 10 years' experience (indeed general practice is about the only branch of medicine in which experience is not rewarded)

Again, whatever his capacity, any doctor can surely give a better service to 2500 patients than he can to 3500 Moreover, an incentive to reduce his list would encourage him to take in a partner, or form a group practice Similarly, good premises and equipment, though no guarantee of good work, are essential tools for the job

A fourth element, to form the incentive side to such an award, is more difficult to define I suggest that it should amount to an expression of willingness on the part of the individual to maintain his efficiency This would take different forms Some like to take refresher courses Others prefer to engage in research or to be clinical assistants at nearby hospitals—or to engage in some other form of postgraduate training The essential thing I suggest is that, to qualify for such an award, the doctor would have to bring evidence of his efforts to improve his efficiency in one way or another I see no harm in the idea that such evidence should be produced again, say, every seven years—so that the grass shall not grow, &c

Stratford-on-Avon
E O EVANS

CARDS FOR PATIENTS TAKING STEROIDS

SIR,—It is recognised that sudden withdrawal of steroids in patients undergoing long-term treatment may be dangerous, particularly when such patients have been subjected to sudden stress, such as an acute illness, accident, or emergency operation In these circumstances it may be of vital importance for the physician or surgeon responsible for the patient's immediate care to be made aware that the patient has been on steroid therapy, the form in which it is being administered, and the daily dose

The education subcommittee of the Empire Rheumatism Council gave this matter consideration at a recent meeting and reached the conclusion that a useful purpose would be served by the issue of a card to patients receiving steroids, stating the preparation in use and its daily dose The hospital or clinic supervising the patient's treatment and the name and telephone number of the family doctor should also be recorded along with simple instructions to the patient.

I have been instructed by my committee to bring this matter to your notice, as the Empire Rheumatism Council would be prepared to make a supply of these cards available to any physician who might wish to use them

J J R DUTHIE
Chairman,
Education Sub-committee,
Empire Rheumatism Council

Faraday House,
8-10 Charing Cross Road,
London, W C.2

VENTRICULAR SEPTAL DEFECT

SIR,—Your leading article of July 12 favours a classification based primarily on catheter studies and necropsy Open heart surgery enables one to obtain a more physiological appreciation of the anatomical defects, 36 ventricular septal defects have been repaired in the past year at this hospital and as a result it is suggested that the presence or absence of an infundibular pulmonary stenosis plays a major part in the pathological physiology of ventricular septal defects, and that therefore this factor should be included in such a classification

Full cardiac catheterisation figures and operative details are available on 22 of these 36 cases They suggest that the following classification be used

(1) The pulmonary-artery pressure, right ventricular pressure, and systemic pressure are of a similar level These cases have no obstruction to a shunt of blood from the left ventricle to the right ventricle, and they have no obstruction to the outflow tract of the right ventricle

The cardiac catheter passes with ease into the pulmonary artery At surgical repair, though there may be some work hypertrophy of the infundibular muscle, the outflow tract is adequate and no resection of muscle is required

We have had 12 such cases, with 4 deaths

(2) The pulmonary-artery pressure is low, the right ventricular pressure high, approximating to the left ventricular pressure No cyanosis is present

These cases are frequently referred to as an "acyanotic tetralogy of Fallot" The cardiac catheter may pass with some difficulty into the infundibular chamber and at surgery the physiological barrier of muscle which protects the lungs from the raised ventricular pressure may be seen. Resection of this infundibular stenosis is a requisite part of the operation, coupled with repair of the ventricular defect

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[6] Hurst, A F *Guy's Hosp Rep* 1921, 71, 26
[7] Moscheowitz E *Amer J med Sci* 1943, 206, 576
[8] Murray, C. D *ibid* 1930, 180, 239
[9] West, R *Lancet* 1946, ii, 899
[10] Burdon, J F *Brit med J* 1958, ii, Suppl. p 27

6 cases with 3 operative deaths

(3) The pulmonary-artery pressure is low and the right ventricular pressure is low The systemic pressure is normal

These are the small muscular defects of the maladie-de-Roger type We have had 4 cases, no deaths

The inclusion of the second group of cases, the "acyanotic tetralogy of Fallot", under the heading of ventricular septal defect is warranted by the fact that group I and group II merge into one another They are both amenable to surgical treatment This differentiates them from the advanced cases of Fallot's tetralogy where the pulmonary artery is of small size and which, even after repair of a ventricular defect and removal of any right outflow-tract obstruction, may well be unable to take the increased flow of blood

Department of Surgery,
Stanford University School of Medicine

A G NORMAN

NO MORE NEOLOGISMS ?

SIR,—We are grateful to you for your defence of necessary neologisms Indeed, we find Sir George Pickering's criticisms (July 26) of the use of "hæmorheology" a little difficult to follow

It is, of course, true that many great men have studied the flow of blood and the mechanical properties of blood-vessels before a special term for this field of work was needed But surely many doctors must have tried to find causes and cures for diarrhœa and amenorrhœa long before the Greek root "rheo" was so happily introduced to describe these conditions Moreover, Sir George, although quoting our definition for hæmorheology, appears to restrict this term to "the blood-flow in relation to the vessel wall", thus overlooking the fact that much more than this is implied

Rheology, the science of the deformation and flow of matter, forms a part of the official title of scientific societies in many countries The Third International Congress on Rheology will be held in Germany in two months' time The name of this branch of physics is almost identical in all four of the official languages of that congress—English, French, German, and Russian—and, of course, in many other languages Few people can fail to know the meaning of the root "hæmo" The combination of these two Greek roots seems to be indicated if we are to be saved the nuisance of continually repeating the full definition of this branch of science

We, as hæmatologist and rheologist respectively, therefore, move that the term "hæmorheology" be accepted as a very necessary neologism

Medical Research Laboratories,
Charing Cross Hospital,
London, W C 2

A L COPLEY

National Institute for Research
in Dairying,
University of Reading

G W SCOTT BLAIR

SIR,—Sir George Pickering and Dr Pappworth (July 26) raise the question of an ever-expanding, often grammatically objectionable, medical terminology I would emphasise that these two aspects—the tendency of new terms to increase with time, and the suitability of the new word—must be kept distinct in our minds, especially when we reach the point of protest

The first reflects, surely, an inherent characteristic of (scientific) development in general Discoveries in all fields of medicine bring with them new names and we *have* to welcome them! But also, and this is of at least equal importance, the reappraisal of a difficult problem may be a perfectly good reason for a new word, which, when coined, helps to focus and integrate the new notion

Just as the new terms come into use the old ones go into disuse and the survival of a new term depends entirely on the mood, tastes, and existing needs of the people for whom it was intended Beneath this normal mechanism of word production, however, there seem to act, especially during the last few decades, gross exaggerative undercurrents due, I suspect, to three main reasons

(*a*) Specialisation tends to take the form of a closed cult and all new members have to go through a period of initiation in which the apocryphal words of the cult must be mastered, clearly, such words have a high magical value (for they signify the concentrated wisdom of the "specialty"), become irresistible in their perpetual use, dominate the predisposed members of the cult, and, in moments of mystical ecstasy, may lead to new products—Greco-Latin hybrids, or even full blown neologisms should the right mutation take place

(*b*) Words which are quite unknown, or at least difficult to understand with certainty,–foreign phrases and proverbs, Latin-Greek-French-German-or-Oriental-medical-terms, and their hyphenated permutations, have such an appeal that their use in a medical paper appears to strengthen its importance, repel criticism and, perhaps, make its publication a little more probable In this respect also, some writers seem to aspire to associate their names with the introduction of a linguistic novelty, thence the abundance of terms like cephalalgia rather than headache

(*c*) A neologism perpetrated in Greek, Latin, Greco-Latin, &c , is permissible if not advisable, a neologism in one's own language—a strangely difficult thing—is usually considered as an ominous sign of a very serious mental disease

I have not drawn any semantic boundaries around the words jargon, neologism, neology, term, nomenclature, or even barbarism I expect Professor Pickering might enlarge upon this in his promised communication on the matter, such a semantic tidying up will put things in their right perspective and, I hope, might substantiate my foregoing views about the natural production of scientific words and the unnatural exaggeration of the present day towards jargon (i e , towards terms known only to members of a certain group)

Another point that may well emerge from such a study is that when medicine stopped being written in Latin, a conscious effort was made by the doctors of many countries to introduce in their scientific languages terms of Greek or Latin origin with the view to continuing a sense of international understanding in the writings of medical men Such terms (e g , catagma) still appear in medical dictionaries but are completely out of use and should not be confused with the tendency to create jargons—a much more complex phenomenon

Turning to the "suitability" of the new word, *it is here* that the most striking monstrosities are perpetrated against clarity, elementary etymology, and euphony The first two are, of course, more important and mistakes in them are invariably due to ignorance of the *materials employed* To take the example Professor Pickering wants (so very understandably) to challenge, Dr Copley having studied the properties of blood-flow and factors affecting it, felt the need for a comprehensive and precise term for this subject, thus, "hæmorheology" was coined, clearly of Greek material The word the Greeks have for "the flow", however, is not—*rheo* (‘ρεω = I flow) but ‘ροη, which should of necessity be transliterated as "rhoe" This probably appears much like roe and perhaps unsavoury for the occasion

I want to emphasise that this type of offence of being obscure and linguistically inaccurate is almost lost in the wave of the much more serious offence of substantial error natriuresis, (which Professor Pickering quotes) simply means "excretion of sodium" and not "increased excretion of sodium" which the author wanted to say "Kaluresis" is doubly wrong for, at least, it should read "kaliuresis" if not "hyperkaliuresis" which is the accurate, although not welcome, term

From Dr Pappworth's interesting anthology, about 52% of the first list are legitimate, though perhaps not generally used terms, the words neurosophical, dysraphicus, undervascularised, transfusionist, and thoracologist are just clumsy and/or obscure while allergology and ataralgesia are linguistically wrong (they "mean" allergiology and ataraxalgesia)

I do not think I can agree with Dr Pappworth's views on the suffix -itis "Inflammation" is quite accurately translated from Greek in which *φλέγμα* means flame, heat, in inflammation, therefore, redness and swelling usually follow (Hence *φλεγμαινειν* also means "to fester") The looseness of the suffix -osis or -pathy is, I feel, well in line with our increasing knowledge of the conditions to which they are attached

Few would disagree with your view that Natural Selection is a decisive factor in the fate of neologisms But how about jargon? There is much more there than the venturing of an epithet or the display of simple affectation Not only it reflects psychological reactions (some of which I half-humorously mentioned before) but it possesses some of the dubious virtue of scientific "shorthand," at a moment when science is getting more and more longhanded Professor Pickering and all academic teachers can fight jargon mostly by their own example, expressing their views simply and understandably, so that clarity replace undesirable jargon in all medical branches

The Maudsley Hospital,
London, S E5

G M JACOBIDES

SIR,—As an addendum to my letter of July 26 I should like to include the following words, taken from *The Lancet* during 1958

Typology
nomothetic
electroplexy
renoprival
natriuresis
chloruretic
hepatocerebral
immunoconglutinin
reticulohistiocytosis
proteinosis

Immunoconglutinin and reticulohistiocytosis represent two of the ugliest polysyllabic artificial neologisms ever perpetrated

Natriuresis and chloruretic are two of the words singled out by Sir George Pickering (July 26), and renoprival suggests that renal specialists are amongst the worst offenders A *Lancet* article of 1957 contained the word nephritogenic, which apparently has nothing to do with the creation of kidneys but describes those organisms which cause renal lesions, and *The Lancet* (1952) used the term *tubulorrhexis*

Hiding behind the cloak of somebody else's authorship by putting quotation marks around a word is rarely justifiable, because it often merely perpetuates the use of a bad term Examples of this were the use of the word proteinaceous in that article which discussed proteinosis, and a *Lancet* article of 1953 which contained the word metabolician and another of 1955 mentioned dolichostenomelia and phenocopy, all in quotation marks

In 1954 an author repeatedly used sideropenic where most of us would have used the accepted phrase, iron deficiency And in a more recent article[1] the word clubbing, which was used in the title, was later replaced by acropachy Several questions occur to me

(1) What is the difference between acropachy and pachyairia, another term which I have come across in my reading?

(2) Is acropachy synonymous with clubbing, and, if not, what are the other causes of it?

(3) Does acropachy describe only part of the clubbing phenomenon? If so, what is the purpose in giving the components of clubbing different names?

Another problem which confronts the medical reader is the replacement of well-accepted and known names by new terms which the author thinks more accurate For example the replacement of the term fibrocystic disease of the pancreas by either mucoviscidosis or mucoid dysporia. Some authors, wishing to point out the well-known facts that periarteritis nodosa (first named by Kussmaul and Meir as long ago as 1866) is probably neither inflammatory nor necessarily associated with nodules, have coined the following titles for this disease polyvasculitis, allergic granulomatous angiitis, polyarteritis nodosa, necrotising arteriolitis, hypersensitivity angiitis

Most authors would agree that there are clinical gradations between typical angina of effort and coronary thrombosis Does this justify a new term? I would say, "No" If it does, what should it be? I have come across the following answers. status anginosus, severe angina, angina decubitus, infarction without infarction, prodromal coronary artery occlusion, coronary failure, acute coronary insufficiency, intermediate coronary syndrome Perhaps I am wrong in considering all these are one and the same thing

London, W 1

M H PAPPWORTH

SIR,—There is plenty of room for new words in medicine, and we are all indebted to you for your defence of literary freedom The danger of your journal setting out to "uphold the dignity and purity of the English language" by censorship is illustrated by Dr Pappworth's letter of July 26, nearly all of which can be disputed

It is proper that new concepts and classifications should be borne by new words, untarnished by confusion and misuse What is the alternative? Will it please your correspondents if we give new meanings to old words, and will they prefer the confusion if advances in knowledge slip, half digested, into our minds, disguised in familiar forms We are fortunate in medicine that a technical term is unmistakable, and does not, as often in subjects like philosophy and economics, masquerade as an everyday word or phrase Thus, the reader is made aware of his ignorance, and consequent loose thinking is discouraged

Musicians have complained about their lack of technical terms, and its cramping effect A growing subject needs a fluid language, with words passing freely in and out of common use For example, when "hyperchromic anæmias" were redescribed as "macrocytic anæmias" a rational understanding of these diseases became easier

Perhaps one day we may have an *Oxford Medical Dictionary* on historical principles, showing which words are archaic or obsolete, as well as those that are superfluous, misleading, or so ambiguous as to be unusable in precise writing

The real problem is to avoid new words that are unnecessary or ugly If censorship is unacceptable, there is need for a forum where they can be examined, so that Natural Selection can work quickly Such publicity should discourage light-hearted word-making, and also advertise the useful new words, with their associated advances in knowledge It would also in time clarify the indications for new words Perhaps *The Lancet* could find space for an occasional discussion on these lines

For the ugly or ill-chosen words, prevention is easier than reform (although the history of "valvulotomy" shows that reform is possible) The available reference works (Dorland's *Medical Dictionary*, Ffrangcon Roberts' *Medical Terms*, and Jaeger's *Source Book of Biological Names and Terms*) are not widely known, and their users may produce some very clumsy words indeed Euphony is as important as a meticulous classical derivation, and perhaps we should study the practice of drug firms in naming their products, rather than dictionaries of classics and etymology.

There is need for another Gowers to write on *Plain Medical Words*, and show us how to make new ones short and lucid

Glasgow

C MACKENZIE GRANT

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[1] Freeman, A. G , *Lancet*, July 12, 1958, p 57

THE PREDICAMENT OF THE BLADDER

SIR,—We have thoroughly enjoyed Mr Downie's letter of June 21 His warm sympathy for this " unfortunate organ " is entirely understandable As a matter of fact, of course, the various fates to which the bladder is subject represent merely a portion of the ills to which the genitourinary system as a whole is heir Mr Downie might be interested in a statement made some time ago by a philosophic friend of ours, who remarked that the poor design and mechanical construction of the system may be used as an argument in favour of polytheism When asked why, he explained, " It was obviously designed by a *committee* of gods "

D L OPDYKE
F H SNYDER
J G VOSS

Cincinnati,
Ohio

Obituary

ALFRED ARTHUR EDWARD NEWTH
O B E , M B Lond , D P H

Dr Newth, formerly principal school medical officer for Nottingham, died on July 30 at the age of 70

He was the son of a general practitioner who practised in Haywards Heath, and he was educated at Epsom College and Westminster Hospital After qualifying in 1911 he held house-appointments at the Westminster Hospital, and at hospitals in Wolverhampton and Derby, and in 1914 he was appointed school medical officer to the Nottingham education authority Soon afterwards he joined the R A M C , serving in France, and he did not return to Nottingham till 1918 He remained with the city's school medical service, becoming in due course principal school medical officer, until he retired in 1954 He was appointed O B E in 1952

The care of handicapped children was always his special concern, and in his retirement he showed his practical interest in mental health by becoming a medical officer at the Mapperley Hospital, Nottingham He was a member of the medical advisory committee of the British Council for the Welfare of Spastics He also continued to serve as a valued member of the Ministry of Education's advisory committee Of his long and cordial relationship with the Ministry J E U writes

> " Newth's sound judgment and his exceptional insight into the problems and needs of the handicapped child brought us into frequent consultation and I shall always remember the invaluable help he gave as a witness to the Committee on Maladjusted Children As principal medical officer of Nottingham, he stood at the head of one of the foremost school health services in this country, a service which had been developed by his enterprise and efficiency But his interests covered a much wider field than that of his own county borough He was indefatigable in attending meetings, conferences, and refresher courses, and he did much to inspire his colleagues with his own enthusiasm for the welfare of schoolchildren "

Dr Newth was an able speaker and writer, and the School Health Service Group of the Society of Medical Officers of Health owed much to him as secretary and president Of this work H M C writes

> " Dr Newth was untiring in his endeavours, and his preparation of the papers for the meetings was an indication of his energy and acumen He had an excellent and well-stored brain, and though he was meticulous in details, the memoranda which he prepared for guidance had a lively style So much did his colleagues appreciate his service for the group that a dinner was held in his honour, when a presentation was made to which colleagues from all over the country had contributed.
>
> " His interests were not confined to school health, he played an excellent game of golf and one recalls with pleasure his expert comments on visits to Twickenham He was also a skilled craftsman Despite his knowledge and erudition he was by no means the dull administrator, and his friends will remember his unfailing good humour, tact, and pleasant chuckle "

Mrs Newth is also a member of the medical profession

MALCOLM ARTHUR SMITH
M R C S

Dr Smith, who was an authority on the reptiles and amphibia of Eastern Asia and of the British Isles, died at his home at Ascot on July 24 at the age of 82

He qualified from Charing Cross Hospital in 1898 and shortly afterwards went to Siam For the next twenty-five years he practised in Bangkok where he was medical officer to the British Legation After being attached unofficially to the Court of Siam for some years he was appointed the official court physician In this capacity he saw the celebrated Queen Mother, Queen Saowapa, almost daily He described this part of his life in his book *A Physician at the Court of Siam* (1946)

Throughout his life he was interested in zoology, and particularly in herpetology, and made many field expeditions in the Far East in pursuit of his hobby Over 100 papers on the reptiles and amphibia of the East and later of Great Britain (his book on British reptiles and amphibia is the standard work on the subject) testified to the scope of his knowledge and work Most of his collection of 9000 preserved specimens of amphibians and reptiles he presented to the British Museum of Natural History, where he worked for some thirty years after his return to this country He was for nearly twenty years secretary of the zoological section of the Linnean Society and also the first president of the British Herpetological Society, which was founded in 1947

He married Miss Eryl Glynne in 1921 and had three sons, the eldest of whom is a doctor Two of his sons and his second wife survive him

Sir ARNOLD STOTT

R W B , who was one of Sir Arnold Stott's last house-physicians at Westminster, sent these reminiscences to show " his real stature as a teacher "

> The ward round reached the bed of a patient with spasmodic bronchial asthma and Sir Arnold, having heard the history, asked successively the student, house-physician, registrars, and ward sister " What is in his pillow ?" Nobody knew The next move was dramatic and unforgettable " Sister, your scissors " The pillow was slit open and feathers shaken over the ward round " Feathers " was the only comment—but no-one present could ever forget the ubiquitous role of foreign proteins in allergic disorders On another occasion diarrhœa had been present for some days in a patient having medical treatment for a peptic ulcer The student's history was heard with a slightly impatient air, his examination provoking the response " And what was revealed by digital examination of the rectum ? " Silence followed broken by Sir Arnold, " Sister, a glove " Rectal examination was accompanied by the question " What is a scybalum ? " A further silence, then, incredulously, " You *don't* know ? " A still further silence was broken by a rattling sound as a scybalum was rolled along the wooden floor Crude ? Unnecessary ? Aggressive ?—but then so is disease, and the comfort brought to patients later by those present through awareness of the possible agonies of constipation could be said to justify it
>
> Accurate and economic use of words was another lesson Sir Arnold repeated time and time again " What diet is he having, Dr —— ? "

"A light diet, Sir" Pause, then "Phosphorescent?" Or the cutting interruption when told the fauces are injected "Who injected them?" or when told a patient had a temperature "Everyone has a temperature Do you mean pyrexia?" These remarks were delivered quietly and almost resignedly and never caused personal offence "You have told me the joint is swollen," he said to one student. "Now tell me the degree. Is it slight, moderate, or considerable?"

On one occasion Sir Arnold wrote a prescription putting the wrong date, which was pointed out by sister He turned to the student at his elbow accusingly "You saw me put the wrong date and let me do it." The student replied "Since *you* wrote it how could *I* think it wrong?" Then there was a pause and then "That was a good remark, the first for some time How long have you been on my firm?" At that time a clinical firm consisted of six students and he frowned if anyone tried to tag on "Six is enough for one patient," he once said, "and I haven't enough knowledge for more"

The sad day came when the house job was over It was at the end of tea in Sister's office "I consider you have been a good house-physician," he said, which from him was praise indeed "Slight, moderate, or considerable?" I ventured to inquire "You know the answer to that better than I—but thank you for all your hard work." He smiled, shook hands, and walked away

Lord WEBB-JOHNSON

F R P, who studied medicine at Owens College, Manchester, and at the Middlesex Hospital, writes from Bombay

Lord Webb-Johnson, when he was just Mr Arthur Webb-Johnson, an easy-going jovial young man, was my tutor and guide in surgery Since then, these forty long years and more, we have in a way grown up together, for up to the end of his life we corresponded with each other as colleagues and friends Enough has been said about his good qualities, his professional abilities and public work, but as an Indian, deeply grateful to him for his many kindnesses to a lonely foreign student in his country, I add one more tribute to this great Englishman to whom, along with others such as Sir Victor Bonney, Sir John Bland-Sutton, Sir William Sinclair, and Sir William Fletcher Shaw, I owe all I have achieved in my profession

Appointments

BEGG, ROSEMARY A, M.B Edin., D P H administrative assistant county M O, Kent

BREWERTON, D A, M.D, B Sc McGill, M R C.P, D.Phys Med consultant physician in physical medicine, Westminster Hospital teaching group, London

COLES, H M T, M.D Lond, M.R.C.P, D C.H consultant pædiatrician, Westminster Hospital teaching group, London.

COOPER, C F, M D Lond, M.R.C P part-time consultant physician, Wembley Hospital

HOLLOWAY, J J, M.B, N U I, D P H deputy M O H and deputy principal school M O, Northampton

LLOYD, V A, M B Birm, D P H assistant M O H., Sutton Coldfield area, Warwickshire

THOMPSON, ELEANOR A, M R.C S assistant M O H, north-western area, Warwickshire

Leeds Regional Hospital Board

BENIANS, R G, M.D Cantab, M.R C.P assistant geriatrician (S H M.O), Bradford A and B hospital groups

BIRD, J D, M B Sheff, F F A.R C S, D.A part-time consultant in anæsthetics, Hull and East Riding hospital groups

BURBURY, WINIFRED M., M B Lond, D.P M consultant in child psychiatry, Wakefield and Dewsbury education committees

EASTWOOD, John M B Lond assistant pathologist (S H.M O), Huddersfield hospital group

LEESE, STEPHANIE M., M B, B SC Lond., D.P M part time consultant in child psychiatry, Wakefield and Dewsbury education committees

LITTLE, J C., M.B Brist., M R.C.P E., D P.M consultant in psychiatry, Leeds A and B hospital groups

MATHESON, T S, M B Edin, F R.C.S E consultant in general surgery, Otley hospital group

MOYES, A H, M.B St.And., D P M assistant psychiatrist, Clifton Hospital, York

POLLOCK, A V, M B., B.SC. Cape Town, F.R.C.S consultant in general surgery, Scarborough, Bridlington, Malton, and Whitby hospital group

QUINLAN, A G, M B Lond., F R.C.S. part-time consultant in orthopædic surgery, Scarborough, Bridlington, Malton, and Whitby hospital group

SACKER, L S, M B Lond. consultant in pathology, Hull A and B hospital groups

WILSON, PETER, F R.C.S.E., D O M.S consultant in ophthalmology, Huddersfield hospital group

Notes and News

DISTRICT MENTAL HEALTH SERVICES

EARLIER this year Dr Joshua Carse described in our columns[1] the first ten months' work of the experimental outpatient and domiciliary service which is being offered to mental patients in Worthing The service is based on Graylingwell Hospital, Chichester In a fourth interim report on the scheme he compares the results for the first six months of 1958 with those for the first six months of 1957 (which were also the first six months of the service) The total number of patients has fallen from 721 in 1957 to 657 in 1958 and the number of new patients from 699 to 618 But this reduction is largely among the younger people and the number of patients over sixty-five fell by only 10 Though the care of this group remains one of the problems of the service, Dr Carse is able to report that of the 181 elderly patients referred to the service only 46 were sent into hospital

The success of the service at Worthing, which is 22 miles away, encouraged Graylingwell Hospital to start another district service in Chichester itself at the beginning of this year, and in the first six months 510 patients used the service of whom only 124 were admitted to hospital Together the services at Worthing and Chichester cover three-quarters of Graylingwell Hospital's catchment area, and in the first six months of their joint existence the number of admissions to the hospital was 382 compared with 678 in the first six months of 1956 before the start of the scheme Both at Worthing and at Chichester the services rely heavily on the support of the family doctors who have taken a great interest in the experiment At their request a course of weekly seminars was started in Worthing last May on psychotherapy and the general care of the neurotic patient

University of Cambridge

On June 25 the degree of B CHIR. was conferred on G C Sutton.

University of London

Dr W J H. Butterfield has been appointed to the chair of experimental medicine at Guy's Hospital Medical School

Dr Butterfield, who is 38 years of age, studied medicine at Oxford University and at Johns Hopkins He graduated B.M in 1945 and took the M.R.C.P two years later After holding a junior lectureship in pathology in the University of Bristol, he took up a house-appointment in the Medical Research Council burns unit at the Birmingham Accident Hospital In 1949 he joined the scientific staff of the Medical Research Council He visited the United States in 1950–51 and held a research fellowship at the Medical College of Virginia, to investigate metabolic effects of thermal injury Since his return to this country he has worked at the M R.C clinical research unit at Guy's Hospital His published work includes papers on flashburns and the action of the sulphonylureas in diabetes He was associated with the biological investigations at atomic tests in Australia in 1952 and 1956 and was appointed O B.E in 1953

University of Manchester

The Wellcome Trust has given the university a mobile radiographic and laboratory unit which is to be used by the departments of *rheumatology* and *occupational diseases* for field investigations

Society for the Study of Addiction

At a council meeting of this society, the following honorary officers were elected

President Prof A D Macdonald, *treasurer and secretary* Dr Ellis Stungo, *organiser of meetings* Dr W R Bett

Rockefeller Grants

Recent awards by the Rockefeller Foundation include a grant of $35,000 to a research group at London University studying heredity and genetics in mammals, and a grant of £12,000 to Dr Dorothy Hodgkin of Oxford University for her investigation into the structure of insulin

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[1] Carse, J, Panton, N E, Watt, A *Lancet*, 1958, i, 39

Royal College of Physicians of London

At a comitia of the college on July 31, with Dr Robert Platt, the president, in the chair, Dr Saul Adler was admitted to the fellowship of the college (in absentia). The Murchison scholarship for 1958 has been awarded to Dr L G Whitby The following were elected officers for the coming year

Censors J R H Towers, E R Boland, E R Cullinan, J C Hawksley *Treasurer* R R Bomford *Registrar* Sir Harold Boldero *Harveian Librarian* Sir Charles Dodds *Assistant Registrar* J R Ellis *Library Committee* C E Newman, William Brockbank, W S C Copeman, W H McMenemey *Finance Committee* L C Martin, J F Stokes, J W D Bull

The following were elected to the panel of examiners for the membership examination

Terence East, Donald Hunter, Sir Russell Brain, J Forest Smith, L B Cole, J L Livingstone, A C Hampson, Lord Cohen of Birkenhead, A M Cooke, T C Hunt, H K Goadby, F P Lee Lander, W D W Brooks, S J Hartfall, J G Scadding, M L Rosenheim, Horace Joules, Kenneth Robson, Arthur Willcox, Alan Kekwick, Una C Ledingham, J F Stokes, William Phillips, W Melville Arnott

The following lecturers were appointed

Sir Russell Brain (Harveian orator), Alan Kekwick (Bradshaw lecturer), E J Wayne (Lumleian), W S Peart (Goulstonian), P L Mollison (Oliver-Sharpey), Sir Kenneth Clark (Lloyd-Roberts), J F Brock (Humphry Davy Rolleston), all for 1959, D E Denny-Brown (Croonian), K D Keele (Fitzpatrick), F R Bettley (Watson Smith), J W Crofton (Marc Daniels), for 1960

The following, having satisfied the censors' board, were admitted to the membership

Chrystal H Ashton, B M Oxon , G V Balmforth, M B Lond , J L T Birley, B M Oxon , D F Cappell, C B E , M D Glasg , J R Curtis, M B Lond , C T Dollery, M B Birm , E B D Dowdle, M D Cape Town, D W Evans, M B Wales, K F Fairley, M D Melb , O W Hill, M B Cantab , W B Jackson, M B N Z , J V Jones, B M Oxon , N F Jones, M B Cantab , H R Klein, M B W'srand, R E Lovelace, M B Lond , M W McNicol, M B Glasg , Victor Parsons, B M Oxon , Dorab Jehangir Patel, M B Bombay, J S Pennington, M D Melb , R W B Penman, M B Edin , E V Pieris, M B Ceylon, Alan Pollard, M B Cantab , D H H Pullon, M B N Z , A M Rankin, M B Adelaide, M D Readett, M B Birm , J L Reed, M B Cantab , Shelagh M Richards, M B Sheff , Chava E Rotem, M D Lausanne, H H Shawdon, M B Cantab , C K Simpson, M D Lond , J G Sloman, M B Melb , M A Smith, B M Oxon , A E Stevens, M B Lond , D J Stoker, M B Lond , M W Swallow, M B Lond , A K Thould, M B Lond , G E G Williams, M B Cantab , I V Wilson, M B Durh , John Wilson, M B Durh , Susannah M Woodcock, M B Lond , K J Zilkha, M B Lond

Licences to practise were conferred on the following 125 candidates who had passed the final examination of the Conjoint Board

A R Adamson, Richard Allaye, A J R Anderson, A L Ansdell, J T Aroney, J S Bailey, Ekundayo Abayomi Bamgboye, Jehangir Edalji Banatvala, M D Begley, L S Bernstein, W H Bevan-Thomas, G A Bewley, W M Bodger, P R Brass, R C Bretday, P D G Briggs, F H Brindle, M H Brooke, F T Brough, M H Bull, R W Burt, L J Burton, W D Callum, I G Carnegie Brown, I G Christie, P W Clements, D L Common, Daniel Connan, Edith M Cooke, J C Couve de Murville, P A Cullum, T O Dada, Pauline M H Davidson, N A De Heer, Edna M Dunn, A J Earl, R J Earlam, D J Ellam, R C Evans, R J Evans, R E Fallowfield, Martin Fisher, H J L Francis, Paul Fursdon, H A Garfinkel, P B Garland, P M Gelpke, J M Goyder, John Grant, R S Greenwood, J S Grimshaw, A C Halliwell, J D Hardcastle, D C Harvey, A L Hovenden, Anne T Irvine, Anne Jacques, Sadrudin Alibhai Janmohamed, I N L Johnston, Jane M Jones, Winifred N Kaine, N B Kirkland, Hilda Koilpillai, Leslaw Kwasny, Andrea M D Langford, Reza Larizadeh, N K Leiper, D W Lewis, C M Lissaides, P O Liebling, Maxwell Lindsay, Marion R Liss, T A Lloyd-James, A M Lush, D B Macadam, B J T McAvoy, C E Macdonald, J W Mack, K V Mellor, David Mercer, A R Molyneux, Pauline S Monro, H G Morgan, George Moses, I S Muir, Muhammad Yacoub Najjar, A I Nwabueze, N W Oakley, Kolawole Adeniyi Olafimihan, E O Olurin, S B Omi, B A Omi-Okpaku, E H Osborn-Smith, J D Owen, Glenys R Packer, N D Parkin, M G O Parrish, Bruce Pitt-Payne, D Powell, J N Powell, E B Raftery, M J Ramsden, D J Richards, J M R Ridley, Raj Kishore Saksena, Nanjii Sankarayya, M A Sasson, D C L Savage, Montague Segal, R I D Simpson, Margaret R Skelton, B R T Smith, J M Stephenson, J M Taylor, Geraldine Thomas, J B Traherne, W J Trowell, G L Tullett, Fidelis Nwankwo Udeh, A C Upjohn, Sri Krishna-Cumar Rajakesari Villavarayan, Daphne M Ward, P H Waterfield, W F Whimster, Richard Yeo

Diplomas were conferred jointly with the Royal College of Surgeons of England on the following

D A—Kamal Chandra Agarwala, Abdul Amir Alwan Al-Uzri, Bantwal Raghavendra Baliga, F E Bennetts, E P Berwick, F R Bhupalan, Maryrose E Brewerton, Peter Brine, E F Brooks, Georgina D Brown, T H L Bryson, J G Camilleri, W F Carpenter, Gerald Cartmel, Pamela Channon, F B N Clarke, A J Clement, Elmer Clissold, R J H H Colback, C F Conway, Marian H Dadaczynski, J P Davie, I B Denny, G R Dow, Thomas Dowell, A J F Eberle, N L Edmond, H J Ellis, Myrtle Farquharson, E L Fischer, Frank Fisher, Freda W Fleming, J W Gammie, Deb Narayan Ganguly, M A Gilbert, Heath P Gillespie, G B Gillett, J A M Goodwin, B G H Grant, Ajoy Gupta, Marcus Haase, R L Hargrove, Pamela A Harris, Sylvia K Hepton, Eric Holmes, Bridget A Jepson, H W F Jones, Margaret L L Jones, Olive C Jones, Syed Ahmed Kabir, Karingan Ranganath Kamath Norman Kaplan, Shafiquddin Ahmed Khan, P F Knight, R F Knight, J R Lawrance-Owen, M G Leonard, R N Lewis, J G Lindsay, J H L Lloyd-Thomas, J N Lunn, A J McDonald, Hugh McIntyre, T D M McNeill, Frances M McQuitty, S W McVicker, John Mackett, R E Maclaurin, H A Maher, I M J Muir, Ma Shu Poh, Kamil Mustafa, Manohar Laxman Nene, B E Ohmacht, G D Parbrook, Dawood Ahmed Patelle, Audrey M Peeling, P A Pelham, Margaret E Pickering-Pick, W M Pillow, Lora Y Pratt, P B W Price, Denis Proctor, Arnold Rieck, Brenda K Rimmer, R S Ritchie, Pamela D Roberts, Anna I Robertson, Sheila J B Robertson, R H Robinson, David Saltoun, Betty V Scott, R O Selby, H W Stark, J G Thomson, L G von Thomann, Alice van Waterschoodt, H J White, Anne M Wilson, G R V Worrall, P R Wykes, Ming-Hon Yeung, Roman Zeeher

D C H—J T Binless, D G Cottom

D I H—P G Cannon, Jayanta Kumar Chakravarti, A J Hibell, P G W A Lommerse, H F McElligott, Manzur Ahmad Malik, A C Reith, Maung Myo Tint, J de M Vink

D L O—Lajpat Rai Aggrawal, Badiul Alam, A A Anderson, P J Batchelor, P G A Bloomer, R C Bloomfield, J T Buffin, R M C Butler, Shroff Rama Setty Chandrasekhar, G W S Choa, M G Cox, T J Crowe, C E Gabriel, Dwijendar Prosad Ghosh, D J Godfrey, A N Gorsheim, Rameshwar Lal Gupta, P C Leeson, Brian Livesey, M B Stanton, Brenda L Stather-Dunn, J B Walker

D M R D—Walimuni Wilson Mendis Abeysekera, D M Alexander, Tara Pade Banerjee, D M Brebner, P M Bretland, J A D Briggs, F K Downsbrough, H E Engelbrecht, I H Lawrence, K M Mayo, J G A Monks, Asok Kumar Mukhopadhyay, R M Murray-Leslie, Belgod Krishnaiyengar Narasimha Murthy, Krishnar Pasupathy, E J Pick, R G Pitman, D H Provan, J F Ryan, Muriel E Sidaway, William Wilson, F W Wright

D M R T—Prabhatendu Banerjee, J S Bunting, J C McI Fetterly, G A L G Glazebrook, Nikolaos Halazonetis, Norman MacLeod, Dorothy S Murrell, Sumanaweera Nissanga, T A O'Donnell

D O—D E P Jones

D Path—Thomas Gordon, Charles Isaacson, Hugh Richmond, T G Scott, Dilip Kumar Sen, Geoffrey Taylor, Poothathamby Thillainathan, C A H Trench

D P M—H A Anderson, Margaret L Arden, J K Binns, Asuncion F Cheyne, Marion B Coleman, Mary J Collins, G E Cook, Harutiun Davidian, Margaret McC Dewar, David Duncan, R L Duncan, J P Farrell, P G Fawcett, K M Fraser, Pearl Goddard, H S Greer, J G Hegarty, I A Horton, L C Hurst, Muhammad Said Rasem Kamal, K E Le Page, Jeremy Lister, E B McDowall, Agnes M McGlashan, L E McLoughlin, Beryl Margolis, Robert Middlefell, Helen M P Molony, J S V Mouat, E W P Noall, D P Oakley, R H V Ollendorff, H I H Porcher, S G Rowe, Allan Sinclair, F G Spear, Alexander Stevenson, M H Sunderland, E L Sutherland, R P M Urquhart, P K G Warren, J M Woodforde, A R Worters, W B Wright

D P H—Grace V Andrew, Abdul Wahab Bin Mohamed Ariff, Rosemary A Begg, J T Cecil, G F Devey, Sheila H E Fairweather, Renato Gracias, Charles Harris, V A Lloyd, Mahmoud Hussein Mahmoud, R G Newberry, R A Ryan, Ziyauddir Qamaruddin Shaikh, J B Stafford, A W Tranter, John Waters

Royal College of Surgeons of England

At a meeting of the council on July 31, with Sir James Paterson Ross, the president, in the chair, Sir Reginald Watson-Jones, Prof D M Douglas, and Mr W A Mill were elected members of the court of examiners

Lieut-Colonel R H Robinson, R A M C , was awarded the Mitchiner medal, Wing-Commander W B Thorburn the Lady Cade medal, and Surgeon Commander W E Crocker, R N , the Gilbert Blane medal

A diploma of fellowship was granted to Padmanabhan Narendran

Diplomas and licences to practise were conferred jointly with the Royal College of Physicians on those named above

Society for Applied Bacteriology

The following officers have been elected

President, Mr D A McKenzie, hon secretary, Mr G Sykes (Boots Pure Drug Co Ltd , Microbiology Division, Standards Department, Nottingham), hon treasurer, Mr G Ellis Jones, editor-in chief, Dr S E Jacobs, editor, Dr C A E Briggs, hon publications manager, Mr A H Walters, hon advertising manager, Mr E J Mann, committee, Dr Eve Billing, Prof E L Crossley, Dr J G Davis, Dr N R Knowles, Dr Jane Meiklejohn, Mr C A Scarlett, and Dr M Woodbine

Isaac Wolfson Foundation

Since this Foundation was started in 1955 it has distributed £1,114,000 Its latest gifts include £250,000 to the Westminster Hospital School of Nursing and £25,000 to the British Council for the Welfare of Spastics to build residences and workshops at Beaconsfield

The policy of the Foundation, which has a capital fund of more than £6 million, is to advance education and health in the United Kingdom and Commonwealth with particular reference to "scientific and technological education, building facilities for higher education, youth activities, general medical research, cancer research, and medical, surgical, and nursing services" The board of trustees includes Sir Stanford Cade and Lord Evans

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Surgeon Captain C B Nicholson has been appointed an honorary surgeon to the Queen in succession to Surgeon Rear-Admiral E T S Rudd

The Lancet · Saturday 16 August 1958

CEREBRAL VASCULAR DISEASE IN THE LIGHT OF MODERN TECHNIQUES *

J St C Elkington
M D Cantab , F R C P

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I PROPOSE now to consider some varieties of intracranial hæmorrhage Extradural and subdural hæmorrhage, though both important and interesting, are self-contained subjects which have not been greatly influenced as regards either diagnosis or treatment by the developments of the past ten years I shall therefore omit them and shall confine my attention to subarachnoid hæmorrhage and to intracerebral hæmatomas

Subarachnoid Hæmorrhage

Since the papers of Fearnsides (1916) and of Symonds (1924), the clinical picture of subarachnoid hæmorrhage and its predominant relationship to the rupture of cerebral aneurysms have been generally recognised

It has become customary to use the term " spontaneous " subarachnoid hæmorrhage to differentiate those cases where the bleeding into the subarachnoid space is the primary event from those in which it is secondary—for example, to head injury or to intracerebral hæmorrhage

The clinical picture of subarachnoid hæmorrhage with its dramatically sudden onset of severe occipitofrontal headache, vomiting, shock, alteration in consciousness, and signs of meningeal irritation are familiar, and I do not propose to dwell on them Occasional atypical cases are encountered where the characteristic bloodstained, xanthochromic fluid is found unexpectedly in a patient with less readily recognisable symptoms or is absent in cases that otherwise seem fairly typical, but by and large the clinical syndrome of spontaneous subarachnoid hæmorrhage is a very characteristic one

Since the original papers already referred to, a number of series of cases have been published with a view to establishing the causative pathology of subarachnoid hæmorrhage Before arteriography was available workers depended for diagnosis either on clinical judgment or on necropsy findings The former introduces many possibilities of error The latter inevitably gives a distorted picture since only the cases with a fatal outcome can be examined Even at necropsy the cause of the bleeding may not be clearly established and it is generally believed that, in the process of rupturing, a small aneurysm or angioma may destroy the evidence of its own existence It should also be remembered that an analysis of the relatively selected cases in a surgical clinic is likely to give results that are not strictly comparable with those obtained from a general hospital where the cases are unselected It is thus difficult to obtain a wholly satisfactory estimate of the relative frequency of the many possible causes of subarachnoid hæmorrhage, but it is noticeable that the more searching the investigation, the greater is the importance attached to the rupture of some pre-existing vascular anomaly of which " berry " aneurysms constitute the great majority and angiomatous malformations a small minority

Table I summarises the findings of a number of authors as to the relative frequency of the common causes of spontaneous subarachnoid hæmorrhage It will be seen that with one exception upwards of 75% of proved cases are attributable to ruptured aneurysms

Until about ten years ago the exact cause of a subarachnoid hæmorrhage may be said to have been largely of academic interest A knowledge of the pathology might enable one to hazard a slightly more accurate prognosis, and it was, of course, important that some curable underlying condition, such as subacute bacterial endocarditis, should not be overlooked The occasions on which one could be certain even on which side of the intracranial cavity the bleeding-point was situated were few, and more precise localisation depended on such associated findings as cranial-nerve palsies, focal fits, or evidence of local damage to the brain—e g , dysphasia, monoplegia, or hemiplegia, which, more often than not, were absent

TABLE I—RELATIVE FREQUENCY OF COMMON CAUSES OF SPONTANEOUS SUBARACHNOID HÆMORRHAGE IN REPORTED SERIES

Author and date	No of cases	Mode of proof	Aneurysms (all kinds) (%)	Other causes (%)	Unknown (%)
Taylor and Whitfield (1936)	43	P M	77	5	18
Magee (1943)	58	P.M.	74	Not specified	
Hamby (1948)	47	P M 41 Op 6	93 6	Not specified	
Hyland (1950)	55	P.M	80	Angioma 3 8	16 2
Wolfe (1953)	62	P M	79	10	11
Walton (1956) (series A)	82	P.M	72 1	15 9	12

P M =postmortem examination Op =operation

In the years from 1925 to 1945 treatment of subarachnoid hæmorrhage could only be conservative and consisted of skilled nursing, the judicious use of sedatives and analgesics, and protracted bed rest The only point in dispute was whether repeated lumbar puncture was advisable or not Under these conditions it was generally recognised that the disorder carried a considerable, indeed a heavy, mortality which increased with age after 40 years It was also recognised that death from the initial hæmorrhage usually occurred within one week of the onset of the hæmorrhage and that the dangers of a fatal recurrence progressively decreased after the first eight weeks But precise and reliable figures were hard to come by as few workers could report on a sufficiently large number of cases under their own care, and pooled results even from the same hospital were open to obvious criticism

Of more recent years a number of series sufficiently large and uniform to be relied upon have been reported

In table II are set out the results of a number of inquiries

TABLE II—MORTALITY IN SPONTANEOUS SUBARACHNOID HÆMORRHAGE

Author and date	No of cases	Mortality (%)	Period over which reckoned
Taylor and Whitfield (1936)	81	63	2 mos
Magee (1943)	150	56	2 mos
Hamby (1948)	130 { 98 in 1st attack 32 in subsequent attacks	51·5	
Hyland (1950)	191	53	6 mos
Ask-Upmark and Ingvar (1950)	138	28 43	" In hospital " Including follow-up
Wolfe (1953)	91	57	" In hospital "
Walton (1956)	312	45	" In hospital "

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* The second Lumleian lecture for 1958, delivered before the Royal College of Physicians of London on April 17

in the past ten years with regard to the mortality of subarachnoid hæmorrhage treated conservatively It will be seen that, with one exception, they show a mortality-rate of 45–60% and we are forced to the unpleasant conclusion that at an optimistic estimate a patient with a subarachnoid hæmorrhage treated conservatively has only an even chance of being alive two months later I doubt if it is yet generally recognised among physicians how serious is the prognosis in this condition

Although isolated cases had been reported earlier by Dott (1933) and McConnell (1937) and other surgeons, Walter Dandy (1944a and b) was the first to make a serious attempt to eliminate cerebral aneurysms by direct surgical attack

Although in some of his cases the aneurysm had given rise to subarachnoid hæmorrhage, he was primarily interested in the surgical treatment of intracranial aneurysms rather than that of subarachnoid hæmorrhage itself and his cases were selected for operation because the aneurysms could be localised on clinical or radiological grounds and were judged to be amenable to surgical treatment Cerebral angiography was at this stage still in its infancy, and Dandy (1944a and b) referred to it in critical and even in disparaging terms Dandy not only treated saccular aneurysms of the carotid artery by carotid ligation in the neck but also made a direct attack on a number of berry aneurysms situated at the termination of the intracranial portion of the carotid artery and even more distally

In the past ten years cerebral angiography has forged rapidly ahead, and with the development of the percutaneous technique and of improved contrast media it has yielded valuable results over a wide range of cerebral disorders

As regards subarachnoid hæmorrhage it has provided in many cases, for the first time, a means of determining with certainty during life the exact position and nature of the source of hæmorrhage, thus enabling a direct attack on the bleeding-point to be contemplated

Reporting the results in 461 cases of subarachnoid hæmorrhage investigated during the acute stage by bilateral carotid angiography McKissock (1956) and Walsh (1956) give the following figures

Arterial aneurysms	249 (*54%*)
Arteriovenous malformation	53 (*11 5%*)
Primary intracerebral or intracerebellar hæmorrhage	35 (*7 5%*)
No lesion demonstrated	124 (*27%*)
	461

Of the 124 cases in which no lesion was demonstrated by angiography 93 were chosen for follow-up and 31 were discarded because, for one reason or another, bilateral carotid angiography had not been performed on them. Over a period of up to eleven years the mortality in this group of 93 had been 8%, which may be favourably compared with the generally recorded mortality of about 50% during the first two months after the initial hæmorrhage and a further 20% among the survivors as recorded by Hyland (1950) It must surely follow that if the prognosis in cases showing no lesion by angiography is so much better than the average, those cases having a demonstrable lesion must carry a mortality correspondingly higher than the average

The finding of angiomatous malformations as the cause of subarachnoid hæmorrhage in no fewer than 11% of cases (Falconer [1951] had previously found 6%) was in itself an important advance, for the natural history and surgical handling of these abnormalities are totally different from those of leaking aneurysms, and the prospect of permanent cure in cases satisfactorily operated upon is much greater since there is little, if any, liability to recurrence of the bleeding

In a later paper McKissock and Walsh (1956) reporte that the anatomical distribution of the aneurysms demo strated was as follows

Internal carotid artery at level of posterior communicating artery	25%	82 5
Internal carotid artery at level of bifurcation	12%	
Anterior cerebral and anterior communicating arteries	28 5%	
Middle cerebral artery	17%	
Anterior cerebral artery (distal)	3%	
Multiple aneurysms	7 5%	
On vessels in posterior cranial fossa	6%	
Site not established	1%	

These figures, which are generally comparable to thos given by others reporting the results of angiography an also those derived from postmortem studies, make clear that the vast majority of cerebral aneurysms aris from derivatives of the carotid arteries and that they fa into three main groups—(1) those derived from th carotid artery from its point of entry into the subarachnoi space to its termination, (2) those derived from th anterior cerebral or anterior communicating arterie between the hemispheres, and (3) those derived from th middle cerebral arteries in the depth of the Sylvia fissures (fig 7)

While aneurysms in any of these situations may giv rise to subarachnoid hæmorrhage it would be surprisin if structures so diversely placed were to behave identicall after undergoing rupture or proved to be amenable t identical methods of surgical treatment As we shall see the elucidation of these questions has been one of th chief problems to which writers on the subject have paid attention in the past few years

The first series of considerable size of cases of subarachnoid hæmorrhage from ruptured aneurysms treated surgically was published by Falconer (1950, 1951), who reported a furthe series of 50 in 1956 His first series consisted of 50 cases al proved by bilateral angiography to have cerebral aneurysm which had given rise to subarachnoid hæmorrhage All were treated surgically by one or other form of carotid ligation or by direct attack on the aneurysm or by both Falconer reported a survival-rate of 82% with a satisfactory-recovery rate of 66%, and a mortality of only 18%

He pointed out (Falconer 1951) with apparent justification that, as his series contained a considerable number of recurrent cases, the mortality, had they been treated conservatively, would probably have been in excess of 50% He concluded that all cases of subarachnoid hæmorrhage should be investigated as soon as possible by bilateral carotid angiography and that those in which an aneurysm was demonstrated should be operated upon forthwith It might be contended that, from a physician's point of view, it is unnecessary to pursue the argument into greater detail, but the shortcoming of this paper as a guide to management of these cases is that a wide variety of surgical procedures in different combinations were applied to comparatively small groups of lesions which together totalled only 50, and that no clear indication is given as to the interval between the last hæmorrhage and the operation

In his second series of 50 cases, operated on between 1952 and 1955, Falconer's results showed survival-rate 94%, satisfactory-recovery rate 76%, mortality only 6% (Falconer 1956) It is noteworthy, however, that between the two series there had evidently been an important change in policy Whereas in the 1951 series immediate arteriography was advocated in all cases, in 1956 the optimum time for arteriography and surgery was considered to be about the end of the first week after the hæmorrhage This means that the mortality figures of the two series are not strictly comparable, since in that critical week there must have been a considerable number of deaths from the immediate effects of the hæmorrhage, and so the surgically treated cases represented a more selected group from which those carrying the worst natural prognosis had already been eliminated by death

In 1953 Norlen and Barnum published a thoughtful paper

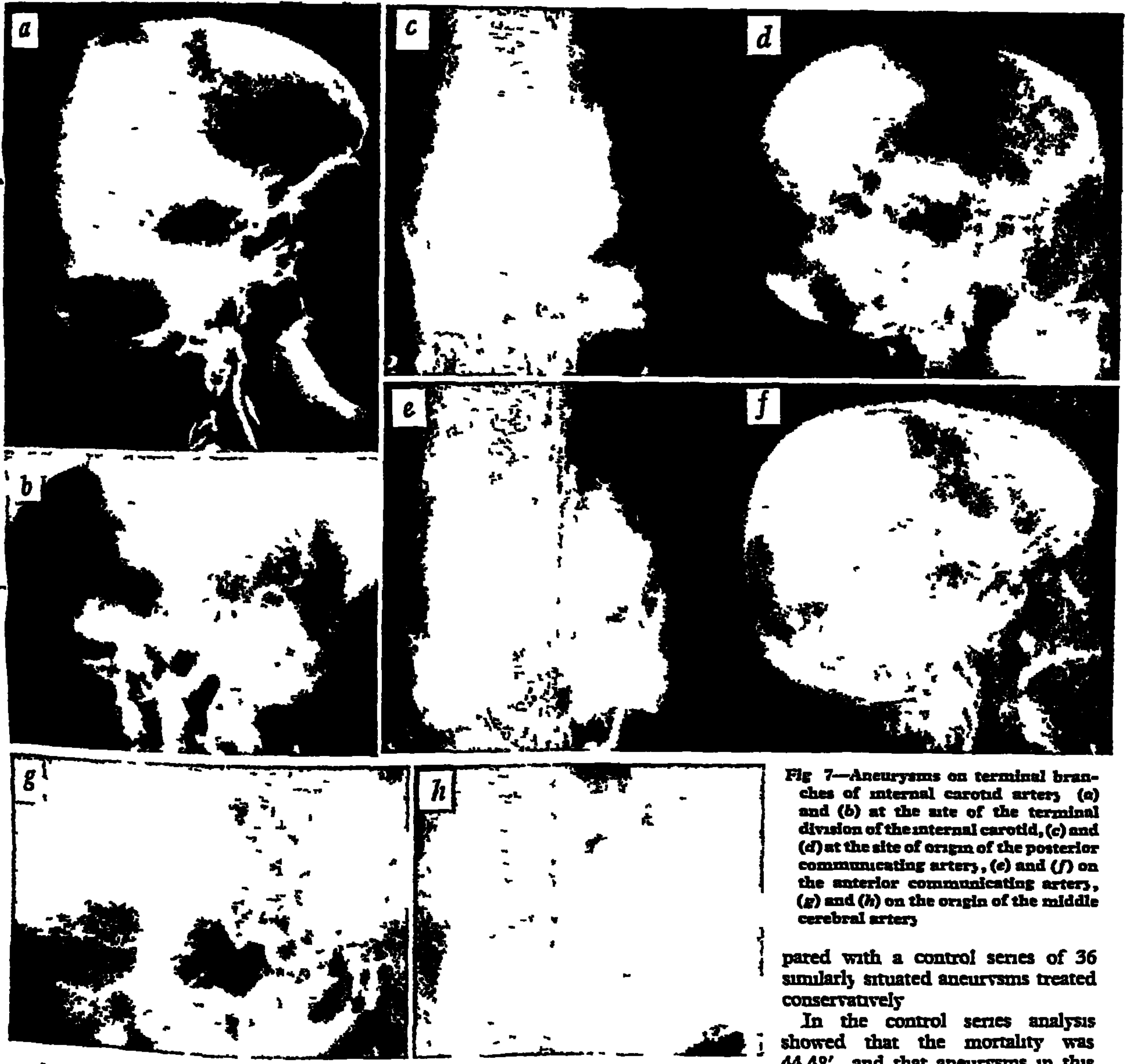

Fig. 7—Aneurysms on terminal branches of internal carotid artery (*a*) and (*b*) at the site of the terminal division of the internal carotid, (*c*) and (*d*) at the site of origin of the posterior communicating artery, (*e*) and (*f*) on the anterior communicating artery, (*g*) and (*h*) on the origin of the middle cerebral artery.

on the surgical treatment of aneurysms of the anterior communicating artery in which they stressed the fundamental importance of the time factor and recognised that two separate problems were involved—namely, treatment in the acute stage of hæmorrhage and treatment in the free interval to minimise the danger of further hæmorrhage. Of their 26 patients, 24 had come under observation on account of a subarachnoid hæmorrhage. 24 were submitted to direct surgical attack on the aneurysm, with 3 deaths (12·5%) at or soon after operation, and another patient died eighteen months later from a further hæmorrhage.

Only 6 cases were operated on within three weeks of the initial hæmorrhage with one operative death, and of these 6 only 4 were operated on within ten days of bleeding.

In 1956 Logue published the results of a more extensive experience in the direct surgical treatment of aneurysms of the anterior cerebral and anterior communicating arteries giving rise to subarachnoid hæmorrhage. He also stressed the importance of considering separately the management of leaking aneurysms according to their anatomical situation and of relating the operative results to the interval between hæmorrhage and surgical treatment.

His series consisted of 37 cases treated by one particular type of surgical operation—i.e., proximal clipping of the anterior cerebral artery supplying the sac—and the results were compared with a control series of 36 similarly situated aneurysms treated conservatively.

In the control series analysis showed that the mortality was 44·4%, and that aneurysms in this situation seldom kill at their first hæmorrhage but tend to bleed again with fatal results during the six weeks after the initial hæmorrhage, with a peak period in the second week. Of the 20 patients who survived on conservative treatment 4 (i.e., 11% of the whole) were left with severe and lasting disabilities.

Of the 37 cases submitted to surgical treatment the overall mortality was 13·5% as opposed to 44·4% in the control series. Of the 30 survivors, 3 (i.e., 8% of the whole) were left with severe residual disabilities. Putting these figures into terms of functional recovery, of the 36 patients treated conservatively 16 were able to resume a virtually normal life, while for the 37 cases treated surgically the corresponding figure was 24 with a further 3 steadily improving at the time of publication.

From his experience of this well-controlled series of comparable cases treated by a single method, Logue concludes that at present the best treatment of bleeding aneurysms at this site (which represent 20–30% of all such cases) is to investigate them as soon as possible after the initial hæmorrhage and then to operate upon them as soon as the immediate effects of this hæmorrhage have subsided and before there has been time for a recurrence—i.e., about seven to ten days after the initial leakage.

Later in 1956 McKissock and Walsh published their results of treatment of a series of 249 cases of subarachnoid hæmorrhage resulting from verified aneurysms. They also stressed the importance of subdividing such cases according to the anatomical site of the aneurysm and in respect of the time that had elapsed since the last hæmorrhage While recognising that the mortality in cases operated on during the stage of acute bleeding would inevitably be high, they believed and sought to demonstrate that, even so, it was appreciably lower than it would have been in the same cases had they been treated conservatively They also recognised that there was risk of their deductions from their results being distorted by the element of selection, and so compared their operative results not only with a comparable number of their own cases treated conservatively but with the results of other series treated conservatively

McKissock and Walsh do not give the precise grounds on which patients were selected for surgical or conservative treatment but state that the choice was largely determined by the date at which the patient was admitted—i e, whether before or after the date on which a more active policy was embarked upon

They established a routine procedure for cases admitted for subarachnoid hæmorrhage Provided that the patient successfully withstood compression of each common carotid artery in turn for ten minutes, bilateral carotid angiography was carried out In the event of an aneurysm being demonstrated, the appropriate operation according to its site was carried out immediately For the purpose of assessing the operative results the patients were divided into three categories according to their clinical condition, on admission in the case of those treated conservatively, and at operation in the case of those treated surgically

Category A—Comprised patients in danger of dying in the immediate future from the hæmorrhage causing admission This included all cases in coma and semicoma and those with severe neurological signs

Category B—Comprised patients who had completely or partly recovered from the results of the hæmorrhage leading to admission but were within a period of eight weeks from it and so were to be considered in considerable danger of a recurrent and possibly fatal hæmorrhage

Category C comprised patients admitted more than eight weeks after the hæmorrhage and who were thus at only moderate risk of a recurrence (20% according to Hyland's [1950] figures)

Comparing the results of conservative and operative treatment in these three categories, their results were as follows

Category A—In 43 cases treated conservatively the mortality was 90% In 52 cases treated surgically the mortality was 65 5%

Category B—In 48 cases treated conservatively the mortality was 37 5% In 72 cases treated surgically the mortality was 12 5%

Category C—In 17 cases treated conservatively the mortality was 6% In 17 cases treated surgically the mortality was 23 5%

Studying these figures critically one notices that the operative mortality for cases in Category A was 65 5%, compared with 50-60% in published series of subarachnoid hæmorrhage of all types and 90% in McKissock and Walsh's control series of cases in the same category Operation under these circumstances can therefore only be justified on the assumption that the expected mortality for cases falling into category A if treated conservatively is much higher than the average for all subarachnoid hæmorrhages and that the mortality-rate of 90% in McKissock and Walsh's control series is truly representative To me these assumptions seem reasonable but not everyone will agree, and the desirability of operating at the height of hæmorrhage remains sub judice

As regards category B, the operative mortality of 12 5% as compared with that of 37 5% in the control series and the 50–60% overall mortality in published cases of subarachnoid hæmorrhage is convincing and is in conformity with the results of Norlen and Barnum (1953) and of Logue (1956) in respect of one particular group of aneurysms—namely, those arising from the anterior communicating or anterior cerebral arteries

As regards category C, in reference to their mortality of 23 5% in 17 cases, McKissock and Walsh explain that the 4 deaths resulted from recurrent hæmorrhages at two years (1), eighteen months (2), and six weeks (1) after simple carotid ligation and that there were no deaths from the immediate effects of operation They no longer consider carotid ligation alone to be adequate treatment for such cases

Considering their material from the point of view of functional results, as well as survival, McKissock and Walsh point out that of 108 patients treated conservatively 51 (46%) survived, of whom only 1 was severely disabled, whereas in the 141 cases treated surgically 94 (67%) survived but 16 were severely disabled

McKissock and Walsh, using the same clinical categories, then broke down their material on the basis of the anatomical site of the aneurysms, different surgical techniques being employed in respect of aneurysms in different sites In subdividing the cases into so many subsections the numbers naturally become much smaller and conclusions more open to error, but these workers conclude that group for group those treated surgically showed a lower mortality than those treated conservatively

Certain conclusions can legitimately be drawn from these various contributions Firstly, subarachnoid hæmorrhage treated conservatively carries a grievous mortality Secondly, active treatment can be logically applied only after an accurate diagnosis has been made and this involves bilateral carotid angiography, which should be carried out as soon as possible Thirdly, those cases within eight weeks of their hæmorrhage are, in the absence of some special contraindication, best treated by surgical means either by direct attack on the aneurysm or by some variety of carotid ligation Fourthly, if more than eight weeks have elapsed since the last hæmorrhage, conservative treatment is usually to be preferred to surgical treatment The question of whether surgical treatment is indicated during the phase of acute hæmorrhage remains for the future to decide It should be remembered that in none of the series cited was artificial hypothermia generally employed It is now possible, under hypothermia, to cut off the cerebral circulation entirely by clamping the three great branches of the arch of the aorta for up to ten minutes without inflicting lasting damage on the brain, and accordingly it seems almost certain that, within the next few years, further evidence will be forthcoming in favour of early surgical intervention Indeed, in a recent paper Botterell et al (1958) have already described a series of 97 cases of cerebral aneurysm operated upon under artificial hypothermia with compression when necessary of both carotid and both vertebral arteries Of these, 64 were operated upon within seven days of the occurrence of subarachnoid hæmorrhage, with only 19 deaths (30%)

Intracerebral Hæmorrhage

Localised hæmorrhage into the substance of the brain, conveniently referred to as an intracerebral hæmatoma, broadly speaking occurs under two widely different circumstances

(1) By rupture of some pre-existing localised vascular anomaly such as an aneurysm or an angiomatous malformation.

(2) By rupture of an atherosclerotic vessel in a patient suffering from generalised arterial degeneration and usually from hypertension

The second group is the one that raises the more complex questions of diagnosis and treatment

INTRACEREBRAL HÆMATOMAS RESULTING FROM RUPTURED ANEURYSMS

The rupture of a cerebral aneurysm commonly gives rise to a subarachnoid hæmorrhage When, however, the aneurysm is buried within the substance of the brain, as is not uncommon in those arising from the anterior or middle cerebral arteries, some and occasionally all of the shed blood ploughs up the surrounding brain tissue and gives rise to an intracerebral hæmatoma, often of considerable size.

This complication is frequently encountered in the surgical treatment of subarachnoid hæmorrhage, and its presence can often be suspected from the clinical picture of rapidly or slowly developing signs of a space-occupying lesion with papillœdema and other signs of a sustained increase of intracranial pressure and confirmed by the shift of the cerebral arteries revealed by angiography.

It is generally agreed that the presence of a massive intracerebral clot in cases of subarachnoid hæmorrhage is a further indication for surgical intervention at the appropriate time.

INTRACEREBRAL HÆMATOMAS RESULTING FROM ANGIOMATOUS MALFORMATIONS

Intracerebral hæmatomas arising from leaking or ruptured angiomatous malformations present a somewhat different problem. They commonly occur in healthy young adults or adolescents and usually develop somewhat more slowly and less catastrophically than those due to ruptured aneurysms. They may or may not have been preceded by events suggestive of a subarachnoid hæmorrhage or of some space-occupying cerebral lesion—for example, by fits or signs of focal brain disease. According to MacKenzie (1953) 30% of angiomatous malformations present with symptoms of hæmorrhage either subarachnoid or intracerebral or a combination of the two.

The diagnosis of an intracerebral hæmatoma of this type depends upon the clinical findings of a rapidly developing expanding intracranial lesion in an otherwise healthy person, especially if additional features suggestive of hæmorrhage are present. The diagnosis is confirmed by angiography which, in addition to showing evidence of displacement of the cerebral vessels, reveals the characteristic features of the causative lesion.

Such hæmatomas should be treated surgically, at the earliest opportunity, by evacuation of the clot and excision of the angiomatous malformation if this is possible—which it usually now is thanks to the pioneer work of Olivecrona and Riives (1948). The recovery in such cases is usually gratifying in the extreme, as the following case illustrates.

Case 7.—A healthy postman, aged 30, had probably had a fit after a drinking bout when about 18 years of age. From that time he was liable to occasional headaches, but in other respects remained well until three weeks before admission when he suddenly developed a severe frontal headache and within a few seconds was aware of weakness of his left leg. This within a few minutes developed into a complete left hemiplegia. There was no disturbance of consciousness or aphasia but he had retention of urine for five days.

On examination three weeks later he had a severe left hemiplegia but slight voluntary movement was now present at hip and shoulder. The cerebrospinal fluid (C.S.F.) was yellow and under slightly increased pressure. The E.E.G. showed abnormal slow waves in the anterior part of the right hemisphere. A right carotid angiogram revealed a small angioma, just anterior to the central sulcus, deriving its blood from the hypertrophied right anterior cerebral artery. At operation a small angiomatous malformation was found and excised, and an intracerebral hæmatoma was encountered and evacuated leaving a ragged cavity in the brain 5 cm. in depth and 5 cm. in anteroposterior extent.

The patient made an uninterrupted recovery, and five years later his only remaining disability is slight weakness of dorsiflexion of the left foot.

INTRACEREBRAL HÆMATOMAS RESULTING FROM CEREBRAL VASCULAR DEGENERATION WITH HYPERTENSION

Massive intracerebral hæmorrhage in patients suffering from diffuse vascular disease with hypertension is a common and usually a terminal event. In most such cases the hæmorrhage bursts through into the ventricular cavities or on to the surface of the brain, and the bleeding continues until the patient dies. But not all such patients die in the first attack, for evidence of old intracerebral hæmorrhages is often seen at necropsy. Some live on, with varying degrees of disability, until another stroke dispatches them or until they die from some other cause, and they may survive for a long time.

In the past such patients were considered to be beyond human aid and an atmosphere of pessimism hung over their misfortunes, for it was only a matter of time before some further catastrophe overwhelmed them. But today some cases of hypertension can be cured and others can be controlled, and the question therefore arises as to whether anything surgical can be done to mitigate the consequences of such a lesion in patients who survive the initial disaster.

The first problem is clearly that of recognising the presence of an intracerebral hæmatoma, which is by no means easy. The differential diagnosis is usually from cerebral softening through infarction.

The patient is commonly a *middle-aged or elderly* person with the usual features of diffuse arterial disease with hypertension. The onset is often ingravescent, neither as dramatic as with the usual massive hæmorrhage nor as silent as with a thrombosis. Headache is usually severe and depression of consciousness is the rule. There may be bradycardia. These lesions are commoner in the posterior parts of the hemisphere, so the local signs usually include hemianopia and sensory disturbance as well as hemiplegia. Where the major hemisphere is involved severe dysphasia is the rule. After a few days, when a patient with an uncontrolled hæmorrhage is likely to have died and one with a massive softening to be improving, the patient with an intracerebral hæmatoma is still sinking into deeper coma, and papillœdema and other signs of increased intracranial pressure may make their appearance. The C.S.F. is under increased pressure and often xanthochromic and may be lightly bloodstained. Untreated, the patient either expires in coma in the second or third week of his illness or gradually struggles back to a normal level of consciousness and survives with a varying degree of damage to body and mind.

If an intracerebral hæmatoma is suspected its presence can often be confirmed by X-ray examination of the skull, which may show the characteristic shift of the pineal shadow away from the side of the hæmatoma. Alternatively an air ventriculogram may be needed to demonstrate the presence of an expanding intracranial lesion and the hæmatoma may be encountered in performing it.

Surgical evacuation of such hæmatomas has been reported in the literature at intervals since the first was reported by Cushing in 1903, and others later by Russell and Sargent (1909) and by Penfield (1933). But the presence of generalised arterial disease and hypertension has more often been regarded as a contraindication to surgical intervention.

In 1941 Furlow et al. reported 5 cases of intracerebral hæmatoma evacuated surgically, of which 3 were secondary to hypertension. They considered that operation was justified where improvement failed to occur with conservative measures, where symptoms and signs of raised intracranial pressure made their appearance, and where the general condition of the patient's cardiovascular system was not so serious as to contraindicate it. The ætiology and symptoms of intracerebral hæmatoma were fully reviewed by Jewesbury in 1947. In

1953 Diana Beck reported on 6 cases of intracerebral hæmatoma treated by evacuation, of which 5 were associated with moderate or severe arterial hypertension In 1957 Gurdjian and Webster reported 11 cases operated upon, of which 6 were in patients over 50 years of age, and of these 6 patients 4 were hypertensive Kelly (1958) has recently reviewed the clinical features of 34 cases, many resulting from hypertension, with especial reference to the results of surgical evacuation of intracerebral clots

I have come to the conclusion that surgical treatment has an undoubted part to play both as a life-saving measure and as means of minimising the residual disability in certain selected cases of intracerebral hæmorrhage resulting from hypertension in atherosclerotic subjects

Case 8—A business man of 48 had been known for some years to be hypertensive, and four months previously had suffered from transient hæmaturia Six days before admission, while abroad, he woke with severe headache and nausea He became confused and incontinent and developed dysphasia and a right hemiparesis Within four hours he had become semicomatose and was admitted to a hospital from which he was transferred to the National Hospital two days later

On examination he was drowsy but could be roused sufficiently to obey simple commands He was dysphasic, had a right homonomous hemianopia and a virtually complete right hemiplegia with considerable sensory loss The optic fundi showed bilateral papillœdema His heart was enlarged, blood-pressure 170/120 mm Hg, his urine contained considerable albumin X-ray examination of the skull showed the pineal body deviated towards the right, and ventriculography showed a large expanding lesion in the left temperoparietal region From this, old blood was withdrawn, and at operation a large intracerebral hæmatoma was evacuated

He made a steady and uninterrupted recovery On discharge from hospital six weeks later he was fully alert, his papillœdema had subsided, and his right-sided weakness and sensory disturbance and dysphasia had almost disappeared There was still a partial hemianopia and some mental impoverishment

During the next two years he continued to improve and led an active life at home, although he was not able to return to business He then suffered a recurrence of his headache with return of his dysphasia and right hemiparesis, but without depression of consciousness or other signs of increased intracranial pressure His blood-pressure was 180/140 mm Hg He again improved, this time spontaneously, and left hospital little altered by his second attack except for further reduction of his mental capacity Seen in recent weeks, nearly four years after his initial hæmorrhage, his condition remains much the same

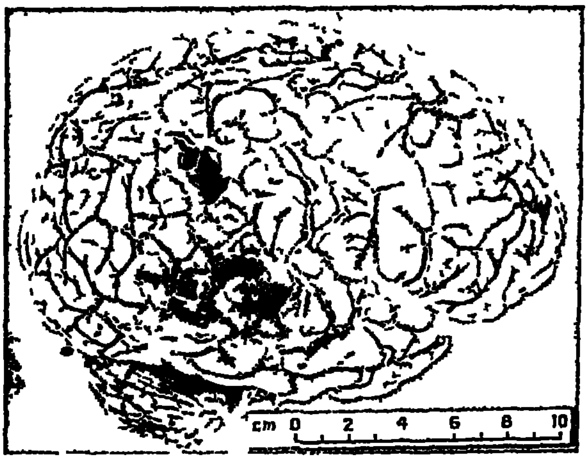

Fig 8—Surface view of the right hemisphere in case 9, showing old bloodstaining of the pia mater over the site of evacuation of an intracerebral hæmatoma

Case 9.—A university lecturer, aged 52, had been known to be severely hypertensive for some years, and over the course of ten years had experienced several hæmatemeses from a pyloric ulcer He was right-handed Three weeks before admission he had experienced sudden numbness on the left side of his face with clumsiness of his left hand, which had cleared up in two or three days Two weeks later he developed weakness of his left arm and leg which rapidly progressed to a complete hemiplegia with increasing drowsiness and severe headache

On examination he had a severe left hemiparesis with sensory loss and a left homonomous hemianopia His fundi showed advanced arterial changes, his heart was enlarged, and his blood-pressure 260/160 mm Hg X-ray examination showed shift of the pineal body to the left, and in attempting ventriculography a blood clot was encountered by the cannula in the right posterior parietal region As much blood as could be withdrawn was aspirated Temporary improvement followed, but as this was not maintained a bone flap was turned down four days later and 20 ml of solid clot was evacuated

From this time his cerebral condition steadily improved, in spite of a further gastrointestinal hæmorrhage sufficiently severe to demand transfusion On discharge two months after admission he was ambulant with a diminishing hemiparesis and hemianopia, and six months after his stroke he was able to return to light duties in his college His blood-pressure remained in the region of 250/150 mm Hg

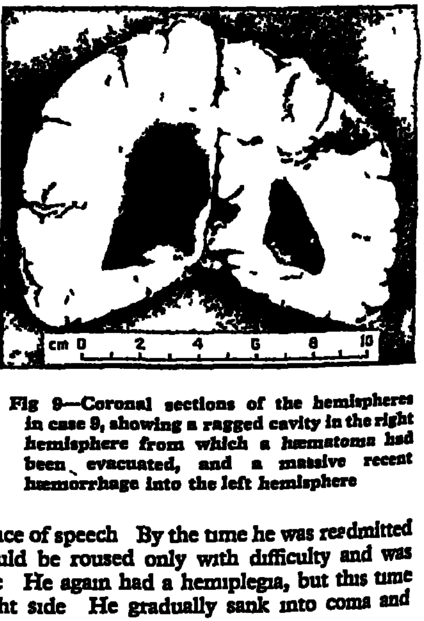

Fig 9—Coronal sections of the hemispheres in case 9, showing a ragged cavity in the right hemisphere from which a hæmatoma had been evacuated, and a massive recent hæmorrhage into the left hemisphere

Approximately a year after his first stroke he suffered a second This came on while he was in bed and was heralded by disturbance of speech By the time he was readmitted to hospital he could be roused only with difficulty and was severely dysphasic He again had a hemiplegia, but this time it was on the right side He gradually sank into coma and died five days after readmission

Necropsy showed evidence of advanced atherosclerosis with cardiomegaly The right cerebral hemisphere showed old bloodstaining under the pia in the right parietal region which was in contact with a well-healed surgical flap in the dura mater and skull An incision in the cortex led to a narrow, ragged cavity in the walls of which there was old bloodstaining The corresponding region of the left hemisphere was occupied by a large recent hæmorrhage which had burst through into the lateral ventricle (figs 8 and 9)

In evaluating these and similar cases we encounter the old difficulty that no-one can say with certainty what would have happened had the patients not been subjected to operation From experience of similar cases I think it is very unlikely that either of those two patients would otherwise have survived the initial stroke, and I am even more certain that if they had been treated conservatively the neurological damage, had they survived, would have been greater Whether the prolongation of life in these cases was desirable or not is a matter of opinion They have been selected for reference because in each case the ultimate prognosis was as bad as it could be, and to many would have constituted a contraindication to any form of surgical treatment.

Conclusions

I have now completed my review and it remains only to draw some general conclusions from it I hope it has been shown that modern surgery and a variety of technical procedures have been brought to bear significantly on the problems of cerebral vascular disease For many years this subject has been at an impasse which has engendered an atmosphere of fatalism and inertia Today there are signs of advance in a number of directions and an attitude of passive acceptance is giving place to one of active inquiry and experiment Although at present modern methods of treatment may only touch the fringe of the problem, it is a growing fringe and every attempt to enlarge it should be encouraged.

This will not be easy, for the idea that cerebral vascular disease is exclusively a medical disorder is deeply ingrained in most of us As physicians we instinctively hesitate to precipitate our patients into the hazards of surgery, the more so in a condition where the initial symptoms we observe are so often both mild and transient A more progressive attitude will give rise to administrative problems The correct handling of cases of cerebral vascular disease will come to depend more and more upon accurate diagnosis This in its turn will necessitate the use of diagnostic procedures which can be carried out only in suitably equipped hospitals which have a highly trained specialist staff available at all times It must, therefore, be expected that a steadily increasing number of cases of cerebral vascular disease will have to be transferred, often at short notice, to specialised centres for investigation and treatment. It is only at such centres that new methods can be tested under satisfactory conditions and advances in treatment achieved Mistakes will inevitably be made, but, bearing in mind the outcome of conservative treatment, we cannot afford to be either timid or complacent

I wish to thank my hospital colleagues for permission to refer to the records of patients under their care, Dr William Blackwood and Dr James Bull for their help in providing pathological and radiological material, and the authorities of the University of California through whose generosity I was afforded the leisure and the facilities without which it would have been difficult to prepare these lectures

REFERENCES

Antoni, N (1941) *Acta med scand* 108, 502
Ask-Upmark, E., Ingvar, D (1950) *ibid* 138, 51
Beck, D (1953) *Arch Middlesex Hosp* 3, 150
Biemond, A (1951) *Brain*, 74, 300
Botterell, E H. (1958) *J Neurosurg* 15, 4
Corday, E., Rothenberg, S F, Putnam, T J (1953) *A M.A Arch Neurol Psychiat* 69, 551
— — Werner, S M (1956) *ibid* 98, 683
Cushing H (1903) *Amer J med Sci* 125, 1017
Dandy, W E (1944a) Intra-cranial Aneurysm New York
— (1944b) Intra-cranial Arterial Aneurysms New York
Denny Brown D (1951) *Med Clin N Amer* 35, 1457
— (1953) *Bull N E. med Cent* 15, 53
Dott, N M (1933) *Trans Med.-Chir Soc Edinb* 112, 219
Eastcott, H H G, Pickering, G W, Rob C. G (1954) *Lancet*, ii, 994
Edwards, C., Rob, C G (1956) *Brit. med J* ii, 1256
Elvidge A R, Werner, A (1951) *A.M.A Arch Neurol Psychiat* 66, 752.
Falconer, M (1950) *Brit med J* i, 809
— (1951) *J Neurol Neurosurg Psychiat* 14, 153
— (1956) *Proc R Soc Med* 49, 166
Fearnsides E G (1916) *Brain*, 39 224
Fisher, M (1954) *A.M A Arch Neurol Psychiat* 72, 187
Foley, J (1956) *Proc Ass Res nerv ment Dis* 35 171
Foley, W T, Wright, I S (1950) *Med Clin N Amer* 34, 909
— — (1956) *ibid* 40 1339
Furlow, W T, Carr A D, Wattenberg, C. (1941) *Surgery*, 9, 758
Gowers W R. (1888) Manual of Diseases of Nervous System Philadelphia
Graham, J G, Maxwell, R D H (1954) *Brit. med J* ii, 1250
Gurdjian, E S, Webster, J E. (1949) *Trans Amer neurol Ass* 74, 50
— — (1951) *ibid* 76, 241
— — (1957) *Arch Surg* 62, 724
Hamby, W B (1948) *J Amer Med Ass* 136, 522.

references continued at foot of next column

DR. ELKINGTON REFERENCES—*continued*

Hultquist, G T (1942) Ueber Thrombose und Embolie der Arteria Carotis Jena
Hunt, J R. (1914) *Amer J med Sci* 147, 704
Hutchinson, E. C, Yates, P O (1957) *Lancet*, i, 2.
Hyland, H H (1950) *Arch Neurol Psychiat* 63, 61
Jewesbury, E C O (1947) *Brain*, 70, 274
Johnson, H C, Walker, A E (1951) *J Neurosurg* 8, 631
Kelly, R. E (1958) *Proc R Soc Med* 51, 209
Krayenbühl, H, Weber, G (1944) *Helv med acta*, 11, 289
Kubik, C S, Adams, R D (1946) *Brain*, 69, 73
Logue, V (1956) *Brit med J* i, 473
McDonald, D A, Potter, J M (1951) *J Physiol* 114, 356
MacKenzie, I (1953) *Brain*, 76, 184
McKissock, W (1956) *Ann R Coll Surg Engl* 19, 361
— Walsh, L (1956) *Brit med J* ii, 559
McConnell, A A (1937) *Zbl Neurochir* 2, 269
Magee, C. G (1943) *Lancet*, ii, 497
Meyer, J S, Leiderman, H, Denny-Brown, D (1956) *Neurology*, 6, 455
— Denny-Brown, D (1957a) *ibid* 7, 447
— — (1957b) *ibid* p 567
Millikan, C H, Siekert, R G, Schuck, R M (1955) *Proc Mayo Clin* 30, 116
Moniz, E, de Lacerda, R. (1937) *Pr méd* 52, 977
Norlen, G, Barnum, A S (1953) *J Neurosurg* 10, 634
Olivecrona, H, Riives, J (1948) *Arch Neurol Psychiat* 59, 567
Penfield, W (1933) *Canad med Ass J* 28, 369
Pickering, G W (1948) *J Amer med Ass* 137, 423
Rob, C. G, Wheeler, E B (1957) *Brit med J* ii, 264
Rose Bradford, J (1908) *Lancet* ii, 703
Rosegay, H., Welch, K (1954) *J Neurosurg* 11, 363
Russell, A E, Sargent, P (1909) *Proc. R Soc. Med* 2, 44
Shapiro, S K., Peyton, W T (1954) *Neurology*, 4, 83
Silversides J L (1954) *Proc R Soc Med* 47, 290
Smirk, F H, Alstad, K S (1951) *Brit med J* i, 1217
Smith, S K (1954) *ibid* ii, 1243
Smyth, G E (1954) *Proc. R Soc Med* 47, 602
Stopford, J S B (1916) *J Anat Physiol* 50, 131
Strully, K. J, Hurwitt, E S, Blankenberg, H W (1953) *J Neurosurg* 10, 474
Symonds C P (1924) *Quart J Med* 18, 93
Taylor, A. B, Whitfield, A G B (1936) *ibid.* 5, 461
Thomson J S G (1954) *Proc. R Soc Med* 47, 602
Walsh, L S (1956) *Acta radiol, Stockh.* 46, 321
Walton, J N (1956) Subarachnoid Hæmorrhage Edinburgh
Welch K., Stephens, J, Huber, W, Ingersoll, C. (1955) *J Neurosurg* 12, 361
Wolfe, H R. I (1953) *Brit J Surg* 50, 319
Wright I S (1955) *Ann intern Med* 43, 942
— Luckey, E H (1955) *in* Cerebral Vascular Disease Symposium of the American Heart Association New York
— McDevitt, E (1954) *Ann. intern. Med* 41, 682

ANTIBODY RESPONSE FOLLOWING INTRADERMAL OR ORAL ADMINISTRATION OF FORMALINISED POLIOMYELITIS VACCINE

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INTRADERMAL vaccination with formalinised poliomyelitis vaccine has been used over the past three years in Denmark, where an estimated 91% of the population between the ages of nine months and forty years have received two doses (von Magnus 1957) Recently Sigurdsson, Gudnadottir, and Petursson (1958) reported their experience with this method in Iceland Since only about one-third the quantity is required for the intradermal as compared with the intramuscular route, its use is important if vaccine is in short supply This paper records an investigation of the efficacy of the intradermal method in young children

Numerous observations have shown that oral administration of certain toxoids or suspensions of killed bacteria can stimulate antibody production (Wilson and Miles 1955) Although this method is far less efficient than parenteral administration, we also decided to attempt immunisation by mouth with killed poliomyelitis vaccine since this is simple

Materials and Methods

British poliomyelitis vaccine 'Polivirin' manufactured by Glaxo Laboratories was used This contains formalinised Brunenders, MEF$_1$, and Saukett strains of polioviruses The methods of administration were

Intradermal—Two doses, each of 0 3 ml of vaccine, were given at four weeks' interval Each dose was halved so that two injections were given into the flexor aspect of each forearm

Oral—Two doses, each of 5 ml, were given in milk at four weeks' interval

Intramuscular—Two doses, each of 1 ml, were given at four weeks' interval

In the first trial, blood samples were taken on the day of vaccination and two weeks later Further blood samples were obtained four weeks after the first dose and four weeks after the second dose In the second and third trials blood samples were obtained on the day the first dose of vaccine was given and again four weeks after the second dose

Tissue-culture techniques and virus-neutralisation tests were similar to those described by Dane, Dick, Connolly, Fisher, and McKeown (1957) Children were considered to have no demonstrable antibody when a 1/4 dilution of sera failed to neutralise 100 TCD$_{50}$ of poliovirus Sera were not titrated beyond a dilution of 1/512 Virus-isolation techniques were similar to those described by Dick, Dane, Fisher, Connolly, and McKeown (1957)

Results

Children of five years of age and under were selected for study since in Northern Ireland they are the age-group most susceptible to paralytic poliomyelitis In the first trial, during May, 1957, 7 children were vaccinated intradermally and 7 others received vaccine by mouth As a control, a further 8 children were vaccinated intramuscularly In the second trial, in November, 1957, 15 children received vaccine intradermally, and in the third trial in January, 1958, another 30 were vaccinated intradermally The age distribution and sex of these children are shown in table I

Intradermal Vaccination

We first studied children who before vaccination were devoid of antibody to all three poliovirus types The antibody response of these triple-negative children four weeks after the second intradermal dose is shown in table II

It will be seen that 3 children devoid of antibody before vaccination remained so and that no child developed demonstrable type-1 antibody

We next studied the antibody response in children who were initially devoid of antibody to one of the three poliovirus types The antibody response four weeks after the second intradermal dose is shown in table III and fig 1

TABLE I—THE AGE DISTRIBUTION AND SEX OF THE CHILDREN IN THE THREE TRIALS

Route of administration of vaccine	No of children in each age-group					Sex		Total
	1–2	2–3	3–4	4–5	5–6	M	F	
Intradermal	12	24	5	8	3	30	22	52
Oral	1	2	3	1	0	4	3	7
Intramuscular	0	4	2	1	1	2	6	8

TABLE II—THE ANTIBODY RESPONSE 4 WEEKS AFTER TWO INTRADERMAL DOSES OF VACCINE IN CHILDREN INITIALLY DEVOID OF ANTIBODY TO ALL 3 POLIOVIRUS TYPES

No of children without antibody to any poliovirus type	No of children with antibody response to			No of children without antibody to any poliovirus type after vaccination
	type 1	type 2	type 3	
5	0	2	2	3

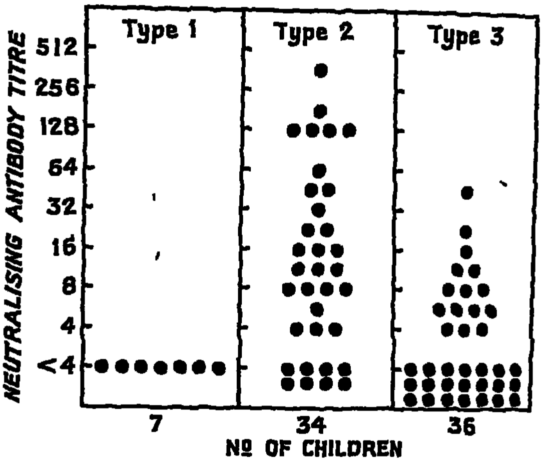

Fig 1—The antibody response 4 weeks after two intradermal doses of vaccine in children initially devoid of antibody to 1 of the 3 poliovirus types

It will be seen that, again, no child produced any demonstrable type-1 antibody The proportion of children producing type-2 antibody was highest The number of children in this age group who were initially devoid of type-1 antibody is small, possibly because of an epidemic of type-1 poliomyelitis in Northern Ireland in the summer of 1957

The antibody response four weeks after the second intradermal dose in children who possessed naturally acquired antibody at the time of vaccination is shown in table IV and fig 2

It will be seen that in most cases the pre-existing antibody is boosted to higher levels by intradermal vaccination. In 3 children the type-1 antibody was not boosted, in 2 the type-2 antibody was not boosted, and in 1 the type-3 antibody was not boosted

Of the control group of 8 children, 5 had no type-1 antibody and 1 had no antibody to any of the three poliovirus types Four weeks after the second intramuscular dose of vaccine only 1 child had not produced any type-1 antibody, while all children of this group showed a type-2 and type-3 antibody response

TABLE III—THE ANTIBODY RESPONSE 4 WEEKS AFTER TWO INTRADERMAL DOSES OF VACCINE IN CHILDREN INITIALLY DEVOID OF ANTIBODY TO ONE OF THE 3 POLIOVIRUS TYPES

Antibody type	No of children without antibody	No of children developing antibody	Percentage antibody response
1	7	0	0
2	34	26	76
3	36	15	42

TABLE IV—THE ANTIBODY RESPONSE 4 WEEKS AFTER TWO INTRADERMAL DOSES OF VACCINE IN CHILDREN ALREADY POSSESSING ANTIBODY

Antibody type	No of children possessing antibody	No of children showing booster response	Percentage antibody response
1	45*	37	93
2	18†	9	82
3	16‡	14	93

* Five had a prevaccination titre of 512 or more and were excluded

† Seven had a prevaccination titre of > 512 and were excluded

‡ One was excluded since insufficient serum was obtained for estimation of type 3 antibody titre

TABLE V—THE ANTIBODY RESPONSE 4 WEEKS AFTER TWO ORAL DOSES OF VACCINE

No of children given oral vaccine	No of children with antibody response to			No of children without antibody response to any poliovirus type
	type 1	type 2	type 3	
7*	1	3	1	4

* A fourth sample of serum was not obtained from one child

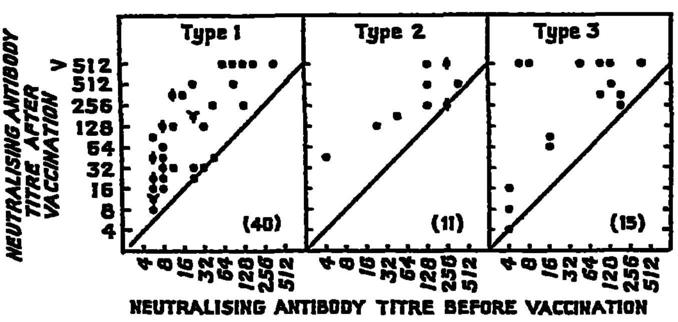

Fig 2—The antibody response 4 weeks after two intradermal doses of vaccine in children already possessing antibody

Oral Administration

The antibody response in 7 children who were given two doses of vaccine by mouth is shown in table V and fig 3

3 children had no antibody to any of the three poliovirus types before receiving vaccine and all failed to develop antibody The number of children responding to type-2 was greater than the number who responded to either type-1 or type-3

After each oral dose of vaccine fæcal samples were collected for ten days to exclude coincidental natural poliomyelitis infection. Because live virus was not detected, it was concluded that the antibody responses in this group were due to the vaccine Children who failed to respond to intradermal or oral administration were later vaccinated intramuscularly

Discussion

In children devoid of antibody to all three poliovirus types there was a poor response to intradermal vaccination (table II) This contrasts with the findings of von Magnus (1957) who in one trial showed that, of 6 children devoid of antibody to all three poliovirus types, 4 developed type-1 antibody and all developed type-2 and type-3 antibodies after two doses of 0·2–0·3 ml of vaccine at four weeks' interval Salk (1955) has shown that the antibody response to vaccination is less in children who are initially devoid of antibody to all three poliovirus types than in those who at the time of vaccination possess antibody to one or more poliovirus types

Again our results show a much poorer antibody response than those of von Magnus (1957) in children who at the time of vaccination were devoid of antibody to any one of the three poliovirus types (table III and fig 1) In the Danish trial of children initially devoid of antibody to one poliovirus type, 21 out of 30 developed type-1 antibody, all of 32 developed type-2 antibody, and 34 out of 35 developed type-3 antibody. Sigurdsson et al (1958) obtained a poor antibody response in Icelandic children who, when vaccinated intradermally, were devoid of antibody

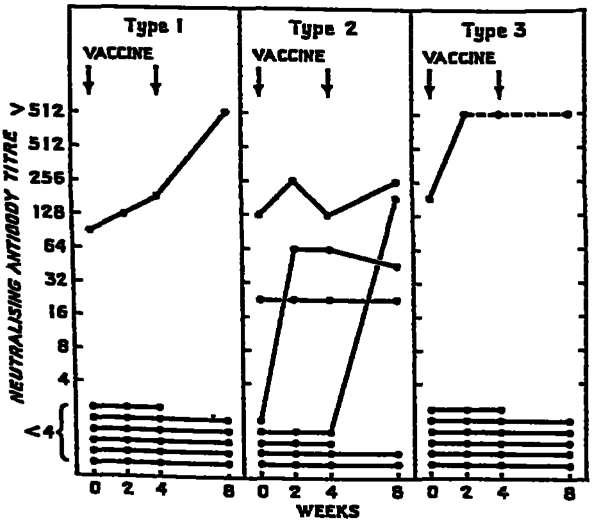

Fig 3—The antibody response 4 weeks after two oral doses of vaccine.

Our results show that in most cases a booster response occurs in children already possessing naturally acquired antibody

In assessing the results of vaccination it is important to know the antigenicity of the vaccine used The British vaccine was tested by the manufacturer and the Medical Research Council before it was released Dr W Wood informed us that, in the batches of vaccine used, the type-2 component was more antigenic than either the type-1 or type-3 component when tested in rhesus monkeys This may account for more children showing a type-2 antibody response as seen in table III and table V Salk (1955), however, has shown that the type-2 antibody response is enhanced by the presence of type-1 antibody and to a lesser degree by the presence of type-3 antibody Of those children vaccinated intradermally who were devoid of type-2 antibody, 27 had type-1 antibody and 8 had type-3 antibody The heightened type-2 antibody response may therefore be related to the presence of type-1 antibody. Salk (1957) has further shown that the proportion of people who respond to a vaccine, and the degree of response, is related to the mass of antigen administered He demonstrated that the booster response to an intramuscular dose of 1 ml. was lower in those who initially had been vaccinated with two intradermal doses each of 0·1 ml at two weeks' interval than after two intramuscular doses of 1 ml He concluded that the intradermal method does not increase the efficiency of the antibody response sufficiently to permit reduction in the quantity of vaccine without sacrificing the effect in people who require more than very small quantities to produce an antibody response While a third intradermal dose of vaccine may increase the number of people who respond (von Magnus 1957) it seems unlikely that the number responding will ever be so large, or the antibody titres so high, as in those who received a greater mass of antigen intramuscularly It therefore appears that, in the absence of a more potent vaccine, the intradermal method has little to commend it for primary vaccination.

The response to formalinised poliomyelitis vaccine by mouth was poor, but the type-2 component appeared to be most antigenic. Because poliomyelitis is primarily an alimentary infection, Sabin (1956), Koprowski et al (1956), Dane et al (1957), and Dick et al (1957) gave living attenuated poliomyelitis vaccines by mouth and antibody was subsequently produced. It is interesting that oral non-replicating polioviruses induced an antibody response in some children, and possibly the response might improve by using a larger dose or a more potent vaccine.

Summary

52 children under the age of five were given two intradermal doses of formalinised poliomyelitis vaccine and the antibody response was studied This method was found to be unsatisfactory for primary vaccination in children initially devoid of antibody Most children who possessed naturally acquired antibody showed a booster response

Although an antibody response occurred in some children after two oral doses of formalinised poliomyelitis vaccine, this method has no practical application at present

We wish to thank the parents who gave consent for their children to take part in these trials, also Dr B R Clarke, Dr Sheila Balmer, and Dr W J McLeod who gave valuable assistance The work was supported by grants from the National Fund for Poliomyelitis Research, the Medical Research Council, and the Northern Ireland Hospitals Authority

One of us (J H C) was in receipt of a fellowship from the National Fund for Poliomyelitis Research during part of this study

REFERENCES

Dane, D S, Dick, G W A, Connolly, J H, Fisher, O D, McKeown, F (1957) *Brit med J* i, 59
Dick, G W A, Dane, D S, Fisher, O D, Connolly, J H, McKeown, F (1957) *ibid* p 65
Koprowski, H, Norton, T W, Jervis, G A, Nelson, T L, Chadwick, D L, Nelsen, D J, Meyer, K F (1956) *J Amer med Ass* 160, 954
Sabin, A B (1956) *ibid* 162, 1589
Salk, J E (1955) *Ann N Y Acad Sci* 61, 1023
— (1957) *Amer J publ Hlth* 47, 1
Sigurdsson, B, Gudnadottir, M, Petursson, G (1958) *Lancet*, i, 370
von Magnus, H (1957) *in* Cellular Biology Nucleic Acids and Viruses (Special Publications of the New York Academy of Sciences), vol v, p 96
Wilson, G S, Miles, A A (1955) *in* Topley and Wilson's Principles of Bacteriology and Immunity, vol ii, p 1274

INSULIN ANTAGONISM IN PLASMA OF DIABETIC PATIENTS AND NORMAL SUBJECTS

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AMONG diabetic patients a group can be recognised in which, besides hyperglycæmia and glycosuria, ketosis and rapid loss of weight usually develop unless insulin is injected In a study of the plasma-insulin activity in these patients using the rat diaphragm technique, it has been shown that, if the blood-sugar level is raised at the time of the test, no plasma-insulin activity is found Moreover, when insulin is added in vitro to the plasma from these patients its activity is apparently inhibited (Vallance-Owen et al 1955)

Plasma from normal subjects shows insulin activity and, when a known amount of insulin is added to the plasma in vitro, the activity of the added insulin is not diminished —i e, there is no measurable antagonism (Vallance-Owen and Hurlock 1954) Nevertheless there is evidence that normal plasma contains an insulin antagonist, the action of which is masked Thus if a normal cat is pancreatectomised, the plasma, which was previously inactive in the rat-diaphragm test, then antagonises added insulin (Vallance-Owen and Lukens 1957)

The experiments reported here were undertaken in an attempt to determine the chemical nature of the insulin antagonist, and to elucidate its mode of action

Materials and Methods

Plasma

Venous blood was withdrawn into a heparinised syringe from non-fasting normal subjects and uncontrolled insulin-requiring diabetics who had received their last injection of soluble insulin at least 15 hours previously The plasma was quickly separated by centrifugation

Salt Fractionation of Plasma-proteins

Sodium sulphate (27% w/v) solution in phosphate buffer (pH 7 8, I=0 1) was added either to the fresh plasma or to reconstituted freeze-dried plasma to give various concentrations of the final solution between 15% and 22% The precipitates were removed by centrifugation, and both fractions were dialysed against distilled water and freeze-dried

Preparation of Albumin

Albumin was obtained from plasma by the trichloroacetic acid-ethanol procedure of Debro et al (1957) In this procedure the 1% trichloroacetic acid (T C A) in 96% aq ethanol is added to 0 5 ml of plasma to a final volume of 10 ml The precipitate is removed by centrifugation, and the supernatant dialysed and freeze-dried Later a modification of this procedure was adopted as follows

An equal volume of 10% T C A (w/v) was added to the plasma, the supernatant after centrifugation was discarded, and the precipitate washed with 5% T C A The precipitate was then suspended in 1% T C A 96% aq ethanol in a volume *equivalent to three times the* original volume of plasma After centrifugation the extract was dialysed and freeze-dried

Characterisation of the Plasma-protein Fractions

The fractions were subjected to paper electrophoresis in 'Veronal' buffer according to the method of Flynn and de Mayo (1951)

Measurement of Insulin Antagonism

Insulin antagonism was determined by the rat diaphragm assay procedure previously described (Vallance-Owen and Hurlock 1954, Vallance-Owen et al 1955)

The freeze-dried fractions obtained were dissolved in buffer solution (Gey and Gey 1936) containing glucose (300 mg per 100 ml) Unless otherwise stated, the salt fractionated plasma proteins were dissolved at approximately the same concentration as they occurred in the original plasma

Insulin was added to the buffer alone and to the buffer with the dissolved fraction to make a final concentration of 1000 micro-units per ml

In any one experiment the glucose uptake of the diaphragm was determined in (*a*) buffer alone (basal uptake), (*b*) buffer plus added insulin (standard), (*c*) buffer with dissolved fraction plus added insulin The uptake was ordinarily measured three times in each solution, diaphragms from three different rats being used

Results

Fractionation of Diabetic Plasma-proteins

As was found previously, full saturation of the diabetic plasma with sodium chloride precipitated the antagonistic activity of the plasma (Vallance-Owen and Lukens 1957) The active precipitate did not contain α_1-globulin but did contain a substantial amount of albumin Owing to the poor fractionation of the plasma-proteins by this method, sodium sulphate was employed in subsequent experiments The activity of the fractions obtained by sodium-

TABLE I—INSULIN ANTAGONISM OF FRACTIONS FROM DIABETIC PLASMA

Fraction	Mean glucose uptake above basal level ± standard error of the mean (mg per 100 ml per 10 mg diaphragm)	
	Buffer + 1000 micro-units per ml insulin	Fraction in buffer + 1000 micro units per ml insulin
Precipitate from 18% sodium sulphate	12 70 ± 0 91 (4)	13 17 ± 1 54 (4)
Supernatant from 18% sodium sulphate		
Precipitate from 22% sodium sulphate	12 68 ± 0 64 (6)	3 02 ± 1 57 (6)
Supernatant from 22% sodium sulphate	11 43 ± 1 02 (9)	2 30 ± 1 14 (9)
Albumin		
3 5–5 5%	12 22 ± 1 08 (4)	−0 37 ± 0 23 (4)
1 25%	12 32 ± 1 05 (4)	3 55 ± 0 67 (4)

Number of observations in parentheses

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* In receipt of a grant from the Medical Research Council

sulphate fractionation of diabetic plasma is shown in table I This shows that the precipitate obtained by saturation with 18% sodium sulphate was devoid of antagonistic activity, whereas the supernatant had such activity

Paper electrophoresis showed that the sodium-sulphate fractionation effected a complete separation of the γ-globulin and albumin fractions—i e, all the γ-globulin was in the precipitate and all the albumin in the supernatant. The other globulin components of the plasma were present in both fractions It was concluded that the antagonistic activity was not associated with the γ-globulin fraction

Attempts to fractionate the antagonistic activity of the supernatant from 18% sodium sulphate by higher concentrations of sodium sulphate were not successful (table I) These results were consistent with the idea that the activity was associated with the albumin in the diabetic plasma. Albumin was, therefore, prepared from diabetic plasma by the T C.A.-ethanol method of Debro et al (1957) As will be seen from table I, this albumin antagonised the effect of added insulin. The inhibition of the added insulin was complete when the concentration of albumin in the buffer was between 3 5% and 5 5% which includes the physiological range. When the concentration was reduced to 1 25% there was still distinct antagonism of the added insulin Paper electrophoresis of these albumin fractions failed to reveal any other plasma-protein.

TABLE II—INSULIN ANTAGONISM OF FRACTIONS FROM NORMAL PLASMA

Fraction	Mean glucose uptake above basal level ± standard error of the mean (mg per 100 ml. per 10 mg diaphragm)	
	Buffer—1000 micro-units per ml insulin	Fraction in buffer—1000 micro-units per ml insulin
Albumin (T C.A.-ethanol) 3·5–5 5%	11·43 ± 0·62 (6)	0·50 ± 0·48 (6)
2·5%	12·63 ± 1·04 (3)	6·60 ± 1·01 (3)
1 25%	11 32 ± 0·74	11 17 ± 0·89 (4)
Albumin (ether fractionation) 5%	12 50 ± 1·40 (2)	2 75 ± 0·45 (2)
Albumin (Cohn Fraction V) 3 5%	12·40 (1)	2·40 (1)
Precipitate from 18% sodium sulphate	11 11 ± 0·34 (4)	15·61 ± 0·70 (4)
Supernatant from 18% sodium sulphate	12·42 ± 0·65 (4)	12 15 ± 0 22 (4)

Number of observations in parentheses

Fractionation of Proteins from Normal Plasma

The demonstration of the presence of an insulin antagonist in the albumin from diabetic plasma prompted us to test the activity of a similar protein fraction from normal plasma. As will be seen in table II, this normal albumin in physiological concentration also had antagonistic activity However, unlike albumin from diabetic plasma, a concentration of 1 25% failed to show any such antagonism. The possibility that this activity of normal plasma-albumin is due to a change in the albumin, associated with the T C.A.-ethanol method of preparation, was tested by examining the activity of two samples of ether-fractionated albumin As is shown in table II, these also inhibited the action of insulin One sample of ethanol-fractionated plasma-albumin (Cohn fraction V) had similar activity The possibility that the antagonistic activity was associated with a substance incapable of precipitation with T C.A.—e g, a polysaccharide—was excluded by changing the method of preparation of the albumin. Thus, when the plasma-proteins were precipitated with 5% T C.A and the albumin was extracted from the washed precipitate with ethanol, this albumin was fully active

TABLE III—EFFECT OF THE SUPERNATANT FROM 18% SODIUM-SULPHATE-FRACTIONATED NORMAL PLASMA ON ALBUMIN FROM DIABETIC PLASMA

Fraction	Mean glucose uptake above basal level ± standard error of the mean (mg per 100 ml per 10 mg diaphragm)	
	Buffer—1000 micro-units per ml. insulin	Fraction in buffer—1000 micro-units per ml insulin
Supernatant from 18% sodium sulphate (7%)—1 25% diabetic albumin	12 38 ± 0·70 (4)	3 20 ± 0·69 (4)

Number of observations in parentheses

Since the albumin from normal plasma inhibited the action of insulin and yet the whole normal plasma did not exhibit any such antagonism, it was of interest to test the activity of fractions obtained from normal plasma by treatment with sodium sulphate. It will be seen from table II that, in contrast with the results with diabetic plasma, the precipitate obtained with 18% sodium sulphate stimulated the activity of insulin, and this supernatant was devoid of antagonistic activity Since the amount of albumin in the supernatant would suffice to inhibit completely 1000 micro-units per ml of insulin, it appears that normal plasma contains a substance which counteracts the antagonistic activity of the albumin This substance could be insulin itself

Effect of Fractions from Normal Plasma on Diabetic Plasma

The failure of the 18% sodium sulphate supernatant from normal plasma to antagonise the activity of added insulin suggested that this fraction might be capable of counteracting the effect obtained with diabetic albumin. That this was not so will be seen from table III This suggests that the amount of substance with insulin-like activity in this normal plasma fraction is just sufficient to counteract the effect of the albumin present

Nature of Insulin Antagonism by Diabetic Albumin

It seems unlikely that the ability of diabetic albumin to counteract the action of insulin on the rat diaphragm is due to a non-specific action on the metabolism of the tissue, for the following reasons (1) the albumin in these physiological concentrations merely reduced the glucose uptake of the diaphragm to that achieved by the tissue in the absence of added insulin, (2) the addition of large amounts of insulin (i e, 10,000 micro-units per ml.) partially counteracted the antagonism of the albumin. The results of the experiments illustrating this point are shown in table IV

Discussion

These observations suggest that the previously described antagonism to insulin found in the plasma of insulin-

TABLE IV—EFFECT OF THE ADDITION OF 10,000 MICRO-UNITS PER ML. INSULIN TO ALBUMIN FROM NORMAL SUBJECTS

Fraction	Mean glucose uptake above basal level ± standard error of the mean (mg per 100 ml per 10 mg diaphragm)	
	Buffer—1000 micro-units per ml insulin	Fraction in buffer—10,000 micro-units per ml insulin
Normal albumin (4%)*	12 33 ± 0·93 (4)	5·93 ± 0·67 (4)

Number of observations in parentheses

* As will be seen from table II albumin at this concentration completely antagonises the effect of insulin at 1000 micro-units per ml.

requiring diabetics resides in the albumin fraction There is apparently similar antagonism in the plasma-albumin from normal subjects However, the albumin fraction from normal subjects is less active in this respect Bornstein and Park (1953) and Hendley et al (1957) studied the plasma of alloxan-diabetic rats They found that there was antagonistic activity in a lipoprotein fraction Owing to the method of preparation of the albumin used in the present experiments it seems most unlikely that the antagonistic activity is associated with a lipoprotein Moreover, the electrophoretic homogeneity of the T C A.-ethanol albumin preparations excludes the possibility that the activity is due to α_1-globulin The homogeneity of such albumin preparations has been repeatedly studied (e g , Schwert 1957) Thus the activity *described here* would seem to be different from that found by Field et al (1957) in the α_1-globulin fraction of the plasma-proteins of severely ketotic diabetic patients

Taylor (1958) has studied the distribution of insulin in fractions of human serum proteins He finds that the maximal activity is in the region of the α_1-globulin when such proteins are subjected to zone electrophoresis, although insulin-like activity is also associated with the β- and γ-globulins These results agree with ours, and explain why the precipitate obtained with 18% sodium sulphate, which contains all the γ-globulin, some of the β-globulin, but no albumin, stimulates the activity of insulin when isolated from normal plasma, but is without activity when isolated from diabetic plasma The inactivity of the 18% sodium sulphate supernatant from normal plasma is probably due to the insulin associated with the α_1-globulin counteracting the effect of the albumin Taylor also reports that the albumin fractions from human serum were inactive with the rat diaphragm test, although radioactivity studies showed that insulin is bound to the albumin even when isolated by the T C A -ethanol method These results are explicable on the basis that the activity of the insulin bound to the albumin is counteracted by the antagonistic activity of the albumin On this basis it is also possible to explain the difference in activity between the diabetic albumin and the normal albumin, for the normal albumin will have some insulin bound to it, whereas the diabetic albumin will be relatively free of insulin

The question as to whether the antagonistic activity is associated with the albumin per se or whether it is due to some substance bound to it must remain open So far it has not been possible to prepare albumin which is devoid of antagonistic activity, but further work is in hand to elucidate this point

In conclusion it would appear that human plasma-albumin preparations are able to counteract the action of insulin in stimulating the uptake of glucose by the rat diaphragm The difference in antagonistic activity between the fractions from normal and diabetic subjects seems to be due to the presence or absence of insulin or an insulin-like substance We suggest that, whatever the site and mode of action of insulin in carbohydrate metabolism, it has first to overcome the antagonistic activity of the plasma-albumin fraction

Summary

Insulin antagonism has been found to reside in the albumin fraction of plasma from uncontrolled insulin-requiring diabetic patients and from normal subjects

The antagonistic activity of the albumin in whole normal plasma is counteracted by some other substa —possibly insulin

At present it is not known whether the antagonism due to albumin itself or to a substance tightly bound to

We wish to thank Professor J McMichael, F R S , and Prof *Dickens*, F R S , for granting facilities for this work, Dr P Ch wood and Dr R A Kekwick for samples of normal human seru albumin, Miss Barbara Kernot for technical assistance, the Med Research Council for a grant for scientific assistance, and Boots P Drug Co for supplies of recrystallised insulin

REFERENCES

Bornstein, J , Park C R (1953) *J biol Chem* 205, 503
Debro, J R , Tarver, H , Korner, A (1957) *J Lab clin Med* 50, 728
Field, J B , Tietze, F , Stetten, D , Jr (1957) *J clin Invest* 36, 1588
Flynn, F V , de Mayo, P (1951) *Lancet*, ii, 235
Gey, G O , Gey, M K (1936) *Amer J Cancer*, 27, 45
Hendley, E D , Bregman, E , Krahl, M E (1957) *J biol Chem* 228, 459
Schwert, C U (1957) *J Amer chem Soc* 79, 139
Taylor, K W (1958) Biochem J Proceedings of the 374th meeting of
  Biochemical Society (in the press)
Vallance-Owen, J , Hurlock, B (1954) *Lancet*, i, 68
— — Please, N W (1955) *ibid* ii, 583
— Lukens, F D W (1957) *Endocrinology*, 60, 625

ARE IMMEDIATE HISTOLOGICAL EXAMINATIONS OF LUMPS IN THE BREAST USEFUL?

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IT has been noticed in this hospital that the number requests for immediate examination of lumps in th female breast has been slowly increasing Since thes examinations are rather time-consuming for the pathologist and especially for the laboratory technician, a smal pilot survey of one hundred consecutive cases was undertaken to assess their value as a routine method

A questionnaire was drawn up and completed as far a possible by the pathologist and the surgeon concerned in each instance The information requested included, a well as the patient's name, age, ward, &c , the surgeon's diagnosis (with alternatives) before operation and after examination of the operative specimen, and the pathologist's diagnosis on naked-eye examination, on freehand section by Terry's method (Terry 1927, Lendrum 1951), and on examination of frozen sections stained with hæmalum and eosin In all the cases the final diagnosis was established by conventional paraffin embedding and section

Methods and Material

Technique

Malignancy can often be determined by inspection or, more often, by careful palpation The examination of immediate sections either prepared by Terry's method or frozen is facilitated by using a very bright source of light The most valuable microscope objective is the scanning (40 mm x 4, supplied by Watson's of London), this gives an excellent topographical view of the mammary architecture which is so important in this form of microscopy This can be ideally combined with a X6

TABLE I—AGE-DISTRIBUTION

Age (yr)	Present series (100 cases)	Large series (1010 cases)
20–29	2%	7%
30–39	14%	15%
40–49	52%	32%
50–59	19%	18%
60–69	7%	14%
70–79	5%	7%
80–89	1%	1%

TABLE II—DIAGNOSES ON PARAFFIN SECTION

—	Present series (100 cases)	Large series (1010 cases)
Carcinoma	50%	50%
Fibrocystic	26%	15%
Hyperplastic cystic (epitheliosis)	10%	10%
Fibroadenoma	5%	10%
Fat-necrosis	4%	1%
Involutional change	2%	—
Papilloma	1%	4%
Inflammation	1%	3%
Leiomyoma of skin	1%	—

long-focus wide-angle eyepiece (or eyepieces if a binocular microscope is used)—e g , the 'Complec' (Watson) or the 'Telaugic' (Swift)

Age of Patients

The age-distribution of the patients is shown in table I For comparison the ages in a larger consecutive series of breast operations in the Western Infirmary, Glasgow, are also given (Sandison 1958) It will be seen that immediate examination was requested in women of widely varied ages The highest incidence of request falls in the fifth decade of life

Type of Case

Table II shows the final diagnosis, and again the larger series is given for comparison In both series carcinoma accounted for 50% of cases Immediate examination was requested for a higher proportion of lumps which proved to be fibrocystic disease and for a smaller proportion proving to be fibroadenoma, papilloma, or inflammation

Results

Diagnostic Errors of Surgeon

These are shown in table III The surgeon was wrong in 25% of preoperative diagnoses, and a wrong diagnosis of malignancy (16%) was commoner than failure to diagnose malignancy (9%) At operation no opinion was given in 3%, but the diagnostic error was much reduced (9%), and failure to diagnose malignancy (6%) was commoner than wrong diagnosis of malignancy (3%) In 3 of the failures to diagnose malignancy the pathologist's diagnosis was also wrong on naked-eye examination

Diagnostic Errors of Pathologist

These are shown in table IV

Naked-eye examination —The pathologist improved slightly on the surgeon's rate of diagnostic error—6% against 9% Most of these errors were failure to diagnose malignancy (5%), and in only 1% was a wrong diagnosis of malignancy made

TABLE III—DIAGNOSTIC ERRORS OF SURGEON

—	Preoperative	At operation
Number of cases	100	100
No opinion	—	3
Number correct	75	88
Number of errors	25	9
Failure to diagnose malignancy	9	6*
Wrong diagnosis of malignancy	16	3

* In 3 of these the pathologist also was in error on morbid anatomy

TABLE IV—DIAGNOSTIC ERRORS OF PATHOLOGIST

—	Morbid anatomy	Terry section	Frozen section
Number of cases	100	87	89
No opinion	2	1	—
Number correct	92	97	97
Number of errors	6	2	3
Failure to diagnose malignancy	5	1	1
Wrong diagnosis of malignancy	1	1	2

Freehand section stained by Terry's method.—In this technique a freehand section cut with a razor or a safety-razor blade is stained by polychrome methylene-blue In 12% of the cases this technique was not used, because it was thought unnecessary owing to the obvious diagnosis on naked-eye examination It should be remembered, however, that malignant change may be present in association with large simple cysts In 1 other case no section was made, because of technical difficulty, the specimen being a mucoid carcinoma Of the 87 cases examined, in 1 case no opinion was given, and in 2 the diagnosis was wrong in one case a puerperal carcinoma was not diagnosed, because of the predominantly inflammatory picture, and in the other case a large intracanalicular fibroadenoma was misdiagnosed as sarcoma

Frozen section stained with haemalum and eosin —In 10 cases no frozen section was prepared, because it was thought unnecessary owing to the obvious diagnosis on naked-eye examination In 4 of these cases, all cysts, neither Terry examination nor frozen section was considered necessary In 1 other case no section was made, because of the smallness of the specimen and the necessity of conserving tissue for formal paraffin section In the 89 cases examined 3 diagnostic errors were made· 2 of these were identical with the errors made on freehand section stained by Terry's method, in the 3rd, epitheliosis with lipophagic reaction was misdiagnosed as the intraduct carcinoma of Paget's disease

Credits and Debits

Unnecessary mastectomy was avoided in 8 cases in 4 the surgeon had said he would have done a radical mastectomy if immediate examination had not been available, and in the 4 others the intention had been to do a simple mastectomy

In 2 cases unnecessary simple mastectomies were done on the advice of the pathologist in one case for intracanalicular fibroadenoma wrongly thought to be sarcoma, and in the other for epitheliosis misdiagnosed as intraduct carcinoma

In the case of puerperal carcinoma it had already been decided that no further operation was contemplated, and that radiotherapy should be used if the paraffin section showed carcinoma

Time Factors

In 80 cases the time of interruption of the operation averaged 7 minutes On the other hand, the average time spent by the pathologist in 42 cases was 40 minutes In most cases this was accounted for by time spent in waiting for the specimen to be obtained In the other cases the times were not recorded

Conclusions

In 100 consecutive cases of lump in the breast for which immediate histological examination was requested some observations were made Surgical diagnosis of the presence or absence of malignancy was correct in 75% of cases before operation and in 88% at operation Before operation the tendency was to overdiagnose malignancy and at operation to fail to diagnose malignancy The pathologist made the correct diagnosis in 92% of cases on naked-eye examination In 3% of cases the diagnosis reached on Terry section and/or frozen section was incorrect 8 unnecessary mastectomies (4 of which would have been radical) were avoided, but 2 unnecessary simple mastectomies were done despite immediate histological examination It should be emphasised that these examinations were made by ten pathologists as part of their routine duties The results are not claimed to approach those of pathologists who have made a special study of this method

The technique of immediate section does not greatly interrupt the surgeon but is time-consuming (in terms of waiting) for pathologist and technician This is the major economic argument against the method The materials used cost only a few shillings, the bulk of this being the cost of the carbon dioxide used

On balance it seems that immediate histological examination of lumps in the breast is worth while

Summary

100 consecutive cases of immediate histological examination of lumps in the female breast were studied

There is a place for this technique in handling some cases of lump in the breast

I am grateful to my colleagues in the pathology department of the Western Infirmary, Glasgow, for their patience in filling in the relevant questionnaire, and to the surgeons of the Western Infirmary for assisting in this investigation Dr Bernard Lennox compiled the original questionnaire

REFERENCES

Lendrum, A C (1951) *in* Recent Advances in Clinical Pathology (edited by S C Dyke), p 524 London
Sandison, A T (1958) *J clin Path* 11, 101
Terry, B T (1927) *J Path Bact* 30, 573

THYROTOXICOSIS WITH GLYCOSURIA AND ADRENOCORTICAL HYPERACTIVITY

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We have recently seen three men with thyrotoxicosis in whom the excretion of urinary 17-ketogenic steroids was increased Our attention was drawn to the first of these cases because the patient had glycosuria and gynæcomastia The second patient had glycosuria, and when the third presented with glycosuria and gynæcomastia we felt confident that his 17-ketogenic-steroid output would be increased, and this proved to be the case

The exact relation of thyroid to adrenal cortical function has still not been fully determined

In thyrotoxicosis the urinary excretion of 17-ketosteroids has generally been found to be normal or reduced (Engstrom and Mason 1944, Escamilla 1949) Indirect tests of adrenocortical function, such as the eosinophil response to corticotrophin and the insulin-sensitivity test, have been reported to show no abnormality (Hill et al 1950, Hernberg and Lamberg 1955) Levin and Daughaday (1955) found the urinary excretion of 17-hydroxycorticoids to be normal, but they showed that hydrocortisone disappeared from the plasma more rapidly than in healthy subjects

A raised output of urinary 17-ketogenic steroids in thyrotoxicosis appears to be uncommon In an unselected group of eight men and twenty-four women with thyrotoxicosis Levell et al (1957) found the output of urinary 17-ketogenic steroids to be raised in one man and two women (M J Levell, personal communication) In a highly selected group of two men and five women with thyrotoxicosis and diabetes these workers found the urinary 17-ketogenic steroid excretion to be raised in one man and all five women Two of the women were reported in detail by Hubble (1955), the man is case 1 of the present group of cases

The cause of the increased excretion of 17-ketogenic steroids is at present uncertain, and we have carried out studies in our three cases to try and determine its mechanism Our work throws no light on the problem why adrenocortical activity should be increased in some cases of thyrotoxicosis and not in others The findings of M J Levell (personal communication) do not suggest that adrenocortical changes in thyrotoxicosis are more common in one sex than the other, and we feel that the mode of presentation with gynæcomastia in two of our cases has produced a sex bias in this study

Case-records

Case 1 —A miner, aged 41, was seen as an outpatient on April 30, 1956 After a dental extraction 12 months previously he had lost 24 lb (10 5 kg) in weight For 8 months he had felt tired and had little energy He was thirsty, and as a result of an increased fluid intake passed large quantities of urine. He became intolerant of heat and sweated easily For 6 months he had been nervous and tremulous He noticed palpitations, particularly in bed at night, and was short of breath on exercise For 2 months his breasts had been sore. His sister suffered from diabetes mellitus

On examination he was thin, nervous, and sweating, body-weight 129 lb (58 6 kg) Moderate exophthalmos was present The thyroid was moderately enlarged, lobulated, and firm The hands were warm and moist, there was a fine tremor of the outstretched hands Pulse regular, rate 120 per min, blood-pressure 150/70 mm Hg The breasts were slightly enlarged, firm, and tender The nipples were normal, milk could not be expressed The urine gave an orange reaction with Benedict's reagent

Investigations —A radioactive-iodine-tracer test confirmed the diagnosis of thyrotoxicosis, the 4-hour thyroid uptake of iodine was 69 4% of the dose given, and the 48-hour protein-bound iodine 4 36% of the dose given per litre of plasma The 24-hour urinary excretion of 17-ketosteroids was 13 5 mg and of 17-ketogenic steroids 28 8 mg The fasting blood-sugar was 150 mg per 100 ml, 1 hour after the ingestion of 50 g of glucose the blood-sugar was 265 mg per 100 ml, and after 2 hours it was 125 mg per 100 ml Radiographs of the skull and chest were normal The Wassermann reaction was negative The erythrocyte-sedimentation rate (E S R) was 28 mm in the 1st hour (Wintrobe), hæmoglobin 14 0 g per 100 ml

Treatment was with carbimazole 10 mg three times daily by mouth

Admission —He was admitted on Aug 7, 1956, for further studies He was found to be myxœdematous with the typical facial appearance and voice change of this condition The basal metabolic rate was −26% (average of four readings) and the serum-cholesterol 455 mg per 100 ml The 24-hour urinary 17-ketosteroid excretion was 9 1 mg, and that of 17-ketogenic steroids 11 9 mg During the administration of prednisolone 20 mg 6-hourly for 3 days the 24-hour urinary excretion of 17-ketosteroids dropped to 3 9 mg, and the 17-ketogenic-steroid excretion rose to 17 2–25 3 mg The administration of corticotrophin 100 units by intravenous drip daily for 2 days raised the 24-hour urinary excretion of 17-ketosteroids to 34 1 mg and of 17-ketogenic steroids to 87 8 mg The fasting blood-sugar was 105 mg per 100 ml, following the ingestion of 50 mg of glucose the blood-sugar was 224 mg per 100 ml after 1 hour, and 156 mg per 100 ml after 2 hours The patient was discharged on Aug 19, 1956

Second admission —He was readmitted on Oct. 12, 1956, having had no antithyroid treatment in the meantime He was thyrotoxic, the basal metabolic rate was +40% (average of four readings) and the serum-cholesterol 230 mg per 100 ml

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The 24-hour urinary 17-ketosteroid excretion was 14·8 mg, that of 17-ketogenic steroids 31·6 mg. Following the administration of prednisolone 20 mg 6-hourly for 3 days the 24-hour urinary excretion of 17-ketosteroids was 11·5 mg and of 17-ketogenic steroids 10·1 mg. The administration of corticotrophin 100 units by intravenous drip daily for 2 days increased the 24-hour urinary excretion of 17-ketosteroids to 14·7 mg and of 17-ketogenic steroids to 45·8 mg. The fasting blood-sugar was 84 mg per 100 ml, following the ingestion of 50 g of glucose the blood-sugar level was 216 mg per 100 ml after 1 hour, and 105 mg per 100 ml after 2 hours. A further glucose-tolerance curve showed the fasting blood-sugar to be 90 mg per 100 ml, following ingestion of 50 g of glucose the blood-sugar was 264 mg per 100 ml after 1 hour, 156 mg per 100 ml after 2 hours, and 120 mg per 100 ml after 2½ hours.

Progress.—The patient was discharged on Oct 27, 1956, and the thyrotoxicosis has since been controlled by carbimazole 10 mg three times daily. His gynæcomastia has disappeared.

Case 2.—A car deliverer, aged 55, was seen as an outpatient on Dec 24, 1956. He had not been well for about 10 months, during which time he had lost 35 lb (16 kg) in weight. For 9 months he had sweated easily, had been trembly, disliked warm weather, and suffered palpitations with shortness of breath on exercise. For 3 months his eyes had been prominent and occasionally he saw double. He had become nervous and depressed.

On examination he was thin, nervous, and sweating, body-weight 142 lb (64·5 kg). Both eyes, especially the right, were prominent and both eyelids were œdematous. The thyroid was only just palpable, it was smooth and firm. The hands were warm and moist with a fine tremor. He had auricular fibrillation with heart-rate of 116 per min, blood-pressure 140/70 mm Hg. The urine gave a yellow reaction with Benedict's reagent.

Investigations.—A radioactive-iodine-tracer test confirmed the diagnosis of thyrotoxicosis, the 4-hour thyroid uptake of iodine was 67·5% of the dose given, and the 48-hour protein-bound iodine 1·23% of the dose given per litre of plasma. The 24-hour urinary excretion of 17-ketosteroids was 10·6 mg, of 17-ketogenic steroids was 24·8 mg, and of gonadotrophins 8 mouse units. The fasting blood-sugar was 110 mg per 100 ml, following the ingestion of 50 g of glucose the blood-sugar level was 160 mg per 100 ml after 1 hour, and 79 mg per 100 ml after 2 hours. Radiographs of the skull and chest were normal. An electrocardiogram confirmed the presence of auricular fibrillation. The Wassermann reaction was negative. The E S R was 11 mm in the 1st hour (Wintrobe), the hæmoglobin was 13·2 g per 100 ml.

Admission.—The patient was admitted on Jan 15, 1957, for further studies. The basal metabolic rate was −28% (average of four readings) and the serum-cholesterol 245 mg per 100 ml. The 24-hour urinary excretion of 17-ketosteroids was 8·7 mg, of 17 ketogenic steroids 36·5 mg, and of gonadotrophins 5 mouse units. During the administration of prednisolone 20 mg 6-hourly for 3 days the 24-hour urinary excretion of 17-ketosteroids fell to 5·8 mg, and that of 17-ketogenic steroids varied between 23·2 and 42·5 mg. During the administration of corticotrophin gel 20 mg 12-hourly intramuscularly for 2 days the urinary 24-hour excretion of 17-ketosteroids was 9·5 mg and 13·3 mg, and that of 17-ketogenic steroids was 40·5 mg and 47·7 mg. The fasting blood-sugar was 70 mg per 100 ml, following the ingestion of 50 g of glucose the blood-sugar was 204 mg per 100 ml after 1 hour, and 108 mg per 100 ml after 2 hours.

Progress.—The patient was discharged on Feb 5, 1957, and since then his thyrotoxicosis has been controlled by carbimazole. When he was seen as an outpatient on Nov 18, 1957, his auricular fibrillation had ceased and his pulse-rate was 80 per min. He appeared euthyroid and the serum-cholesterol was 250 mg per 100 ml. The 24-hour urinary excretion of 17-ketosteroids was 10·0 mg and of 17-ketogenic steroids 15·4 mg. The fasting blood-sugar level was 100 mg per 100 ml, following the ingestion of 50 g of glucose the blood-sugar was 150 mg per 100 ml after 1 hour, and 60 mg per 100 ml after 2½ hours.

Case 3.—A telephone engineer, aged 48, was seen as an outpatient on Sept 12, 1957. He had not felt well for about 9 months during which time he had lost about 14 lb (6·5 kg) in weight. He sweated a great deal and had become intolerant of warm weather. He felt nervous and trembly, on exercise he was short of breath and had palpitations. He had started to be thirsty, and as a result of the increased fluid intake passed large quantities of urine. For 2 months his breasts had been tender and painful, so that he had to give up wearing braces.

On examination he was nervous and sweating, body-weight 139 lb (63 kg). The eyes were prominent and the eyelids œdematous. The thyroid was impalpable. There was fine tremor of the outstretched hands. The pulse was regular, rate 108 per min, blood-pressure 130/70 mm Hg. The breasts were slightly enlarged, uniformly firm, and tender, the nipples were normal, milk could not be expressed. The urine gave a yellow reaction with Benedict's reagent.

Investigations.—A radioactive-iodine-tracer test confirmed the diagnosis of thyrotoxicosis, the 4-hour thyroid uptake of iodine was 79·8% of the dose given, and the 48-hour protein-bound iodine was 2·34% of the dose given per litre of plasma. The 24-hour urinary excretion of 17-ketosteroids was 15·4 mg and 11·1 mg, of 17-ketogenic steroids 23·7 mg and 27·2 mg, and of gonadotrophins 25 mouse units. The fasting blood-sugar was 83 mg per 100 ml, following the ingestion of 50 g of glucose the blood-sugar was 160 mg per 100 ml after ½ hour, 140 mg per 100 ml after 1 hour, and 75 mg per 100 ml after 2 hours. The serum-cholesterol was 140 mg per 100 ml. Radiographs of the skull and chest were normal. The Wassermann reaction was negative. The E S R was 15 mm in the 1st hour (Wintrobe), the hæmoglobin was 14·2 g per 100 ml.

Treatment and progress.—The patient was treated with carbimazole 10 mg three times daily by mouth, and when seen as an outpatient on Jan 9, 1958, he appeared euthyroid. The gynæcomastia had disappeared. The serum-cholesterol was 280 mg per 100 ml. The 24-hour urinary excretion of 17-ketosteroids was 8·6 mg and of 17-ketogenic steroids 8·2 mg. The fasting blood-sugar was 73 mg per 100 ml, following the ingestion of 50 g of glucose the blood-sugar was 120 mg per 100 ml after 1 hour, and 55 mg per 100 ml after 2 hours.

Discussion

Thyrotoxicosis with exophthalmos is generally regarded as pituitary in origin (Naffziger 1954). In our three cases in addition to a state of thyroid stimulation there was increased excretion of adrenocortical hormones—which suggested that adrenocortical stimulation was also present. In the study of his two cases of thyrotoxicosis with diabetes mellitus and adrenocortical hyperactivity, Hubble (1955) thought that panhyperpituitarism was the primary abnormality. One of the most striking features of our cases was that when a euthyroid or myxœdematous state was reached adrenocortical hyperactivity ceased. This suggested that the thyrotoxicosis itself was the cause of the adrenocortical overaction. Hubble (1955) in one of his cases also found that the adrenocortical hyperactivity decreased once the thyrotoxicosis was under control.

In thyrotoxicosis uncomplicated by diabetes the fasting blood-sugar is normal, but the renal threshold is commonly lowered and rapid absorption of glucose may raise the blood-sugar sufficiently to produce glycosuria (John 1932, Spence 1953). This appeared to be the cause of the glycosuria in the present case 3, and his oral glucose-tolerance curve became normal once the thyrotoxicosis was controlled It was probably also the cause of the glycosuria in case 2, but it was difficult to explain the first fasting blood-sugar of 110 mg per 100 ml and also the fasting blood-sugar of 100 mg per 100 ml once he was euthyroid In patients who have recovered from thyrotoxicosis the incidence of diabetes is greater than in the general population (John 1932) This is unlikely to be of adrenocortical origin as steroid diabetes has been reported to be nearly always reversible once adrenocortical hyperactivity ceases (Frawley 1955) Houssay (1944) has shown that prolonged administration of thyroid extract to normal dogs has no permanent effect on glucose tolerance, but that in non-diabetic partially depancreatised dogs irreversible diabetes frequently results Case 1 as well as case 1 of Hubble (1955) had a family history of diabetes, and the failure of their diabetes to improve once the thyrotoxicosis was controlled may have been due to their being potential diabetics before the onset of thyrotoxicosis

Gynæcomastia in thyrotoxicosis was already known to von Basedow (1848) and more recently has been observed by Sterling (1932), Starr (1935), and Ballinger (1947) One of the cases of Starr (1935) had testicular atrophy, and the case of Ballinger (1947) had undescended testes, but their gynæcomastia only developed with the onset of thyrotoxicosis The gynæcomastia in these two cases, as in the second case of Starr (1935), disappeared following thyroidectomy Gynæcomastia appeared in the present cases 1 and 3 as the symptoms of thyrotoxicosis became prominent, it regressed when the patients became euthyroid on carbimazole Gynæcomastia cannot be regarded as indicating hyperpituitarism and may occur in many endocrine and non-endocrine conditions (Menville 1933, Spence 1953) It can be of purely adrenal origin and has been observed after administration of adrenocortical extracts and deoxycortone (Edwards et al 1938, Laurence 1943)

In our cases there were no features suggesting acromegaly, and estimation of the urinary gonadotrophins in cases 2 and 3 showed their excretion to be within normal limits In our three cases and in the two cases reported by Hubble (1955) only the excretion of urinary 17-ketogenic steroids was increased and the urinary 17-ketosteroids were normal These results suggested hypertrophy of the zona fasiculata, the main secretor organ of glucocorticoids, and a normal zona reticulata, which produces androgens (Landing 1955) Such findings were in agreement with those of Deane and Greep (1947), who in thyrotoxic dogs found the zona fasiculata hypertrophied and overactive, but the zona reticulata unaffected The increased output of 17-ketogenic steroids in our patients was unaccompanied by the usual signs of glucocorticoid overproduction and moon-face, hypertension and polycythæmia were not seen This combination of increased glucocorticoid excretion without the signs of Cushing's syndrome has been shown by Ingle (1952) to characterise the response to stress by the adrenal cortex Such conditions have been observed after surgery and have occasionally been seen in cases of cancer (Hardy et al 1953, Hardy 1953, Jepson et al 1956)

The mechanism of the adrenocortical hyperactivity does not appear to us to be of primary pituitary or of primary adrenal origin, as control of the thyrotoxicosis resulted in normal adrenocortical function This result was achieved by carbimazole, which has no direct action on the pituitary or adrenal It seems clear that the thyroid overactivity acting through the pituitary or the adrenal cortex may have been the fundamental cause of the overactive adrenal cortex This appeared to be the most important result of our investigations It is strongly supported by the work of Deane and Greep (1947), who showed that the administration of thyroid extract to thyroidectomised dogs rendering them thyrotoxic produced hypertrophy and hyperactivity of the zona fasiculata and the zona glomerulosa It seems to us most likely that the effect of the thyrotoxicosis is on the pituitary, being comparable with reactions to other systemic diseases which have been described as inducing an increased output of corticotrophin (Currie and Symington 1955)

Summary

Three cases of men with thyrotoxicosis, in whom a high urinary excretion of 17-ketogenic steroids indicated adrenocortical hyperactivity, are described

All three patients had glycosuria, and two had gynæcomastia

On treatment with carbimazole the patients became euthyroid or myxœdematous, adrenocortical hyperactivity ceased, and the gynæcomastia disappeared

There were no signs of acromegaly or of Cushing's syndrome, and the urinary excretion of gonadotrophins was normal in the two cases where they were estimated

Apparently the primary cause of the increased adrenocortical activity was the thyrotoxicosis, and the adrenocortical hyperactivity was not primarily pituitary or adrenal in origin

We wish to thank Dr H P Brody, under whose care these patients were admitted, for his encouragement, and Mr M J Levell for the steroid estimations

REFERENCES

Ballinger, J (1947) *J clin Endocrin* 7, 566
Currie, A R , Symington, T (1955) *Proc R Soc Med* 48, 908
Deane, H W , Greep, R O (1947) *Endocrinology* 41, 243
Edwards, R A , Shimkin, M B , Shaver, J S (1938) *J Amer med Ass* 111, 412
Engstrom, W W , Mason, H C (1944) *J clin Endocrin* 4, 517
Escamilla, R F (1949) *Ann intern Med* 30, 249
Frawley, T F (1955) *Ann N Y Acad Sci* 61, 464
Hardy, J D (1955) Surgical Physiology of the Adrenal Cortex Oxford
— Richardson, E M , Dohan, F C (1953) *Surg Gynec Obstet* 96, 448
Hernberg, C A , Lamberg, B -A (1955) *Acta endocr , Copenhagen,* 18, 41
Hill, S R , Reiss, R S , Forsham, P H., Thorn, G W (1950) *J clin Endocrin* 10, 1375
Houssay, B A (1944) *Endocrinology,* 35, 158
Hubble, D (1955) *Lancet,* i, 1
Ingle, D J (1952) *J Endocrin* 8, xxiii
Jepson, R P , Jordan, A , Levell, M L (1956) *Brit J Surg* 43, 390
John, H J (1932) *J Amer med Ass* 99, 620
Landing, B H (1955) *Ciba Colloq Endocrin* 8, 52
Laurence, R D (1943) *Brit med J* i, 12
Levell, M J , Mitchell, F L , Paine, C G , Jordan, A (1957) *J clin Path* 10, 72
Levin, M E , Daughaday, W H (1955) *J clin Endocrin* 15 1499
Menville, J G (1933) *Arch Surg* 26, 1054
Naffziger, H C (1954) *Ann R Coll Surg Engl* 15, 1
Spence, A W (1953) Clinical Endocrinology London
Starr, P (1935) *J Amer med Ass* 104, 1988
Sterling, M W (1932) *Rev neurol* 39, 141
vo Basedow, K A (1848) *Wschr ges Heilk* 49, 769

" On the humanitarian view all crime is pathological, it demands not retributive punishment but cure This separates the criminal's treatment from the concepts of justice and desert, a 'just cure' is meaningless On the old view public opinion might protest against a punishment (it protested against our old penal code) as excessive, more than the man 'deserved', an ethical question on which anyone might have an opinion But a remedial treatment can be judged only by the probability of its success, a technical question on which only experts can speak Thus the criminal ceases to be a person, a subject of rights and duties, and becomes merely an object on which society can work And this is, in principle, how Hitler treated the Jews They were objects, killed not for ill desert but because, on his theories, they were a disease in society If society can mend, remake, and unmake men at its pleasure, its pleasure may, of course, be humane or homicidal The difference is important But either way, rulers have become owners "—Prof C S Lewis, *Observer,* July 20, 1958

VAGOTOMY IN HYPERTROPHIC PULMONARY OSTEOARTHROPATHY ASSOCIATED WITH BRONCHIAL CARCINOMA

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Since Hippocrates first described clubbing of the fingers and toes in the 5th century B C there have been numerous descriptions of the condition, including an important publication by Mendlowitz (1942) Some of the underlying pathological causes include pulmonary and cardiac conditions, ulcerative colitis, steatorrhœa, cirrhosis of the liver, roundworm infestation, and, rarely, thyroidectomy (Mendlowitz 1942)

In some cases finger clubbing may be associated with incapacitating hypertrophic osteoarthropathy

The most common cause of severe osteoarthropathy is bronchial carcinoma The proportion of bronchial carcinoma reported as showing painful osteoarthropathy varies from 1–2% (Semple and McCluskie 1955) and 5–10% (Flavell 1956) up to 50% (Alvarez 1948) The incidence is probably well under 5% It is peripheral carcinoma rather than the central tumour which is more commonly associated with osteoarthropathy The peripheral type is a relatively uncommon form of lung carcinoma, and is often a localised lesion involving neither pleura nor hilum It is usually surprisingly small in view of the severity of the symptoms in the limbs

Often a quite astonishing improvement takes place after pneumonectomy or even after local removal of the tumour There is often complete loss of pain within a few hours and the effusions in the joints may improve after a few days The clubbing of the fingers and toes sometimes progressively improves, the nails returning to normal as the nail grows out (Flavell 1956)

The satisfactory results of resection in man are also seen in the dog (Lumb and Carlson 1956) Simple operations have had an equally satisfactory effect on pulmonary osteoarthropathy—e g , ligation of the pulmonary artery on the side of the lesion (Wyburn-Mason 1948) and denervation of the lung hilum in inoperable carcinoma (Brea 1948, Hansen 1954) In these operations division of the nerve-supply was apparently the deciding factor in relieving the joint symptoms, rather than any direct interference with the tumour Following these observations and his own previous results of attempted removal, Flavell (1956) denervated the hilum in two cases of inoperable carcinoma with equally satisfactory results The effect was then tried, in three cases, of simple division of the vagus immediately above the hilum without disturbing the hilar structures, the pulmonary osteoarthropathy in all three cases subsided immediately

In view of the remarkable palliation observed by Flavell, vagotomy was done in two advanced cases of unresectable pulmonary carcinoma with severe osteoarthropathy In one case the osteoarthropathy was so incapacitating, with both hands and feet extremely painful and swollen, that the patient was completely crippled

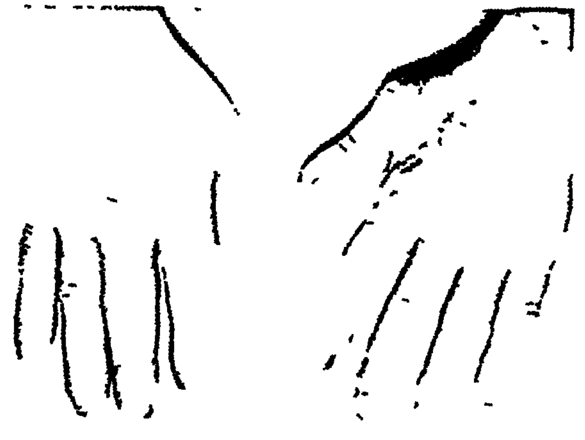

Fig 1—Case 1 œdema of hands and clubbing of fingers

Case-reports

Case 1—A man, aged 64, was admitted to hospital in May, 1956, with advanced pulmonary osteoarthropathy Severe pain limited the movements of his hands, elbows, feet, and knees He was bedridden The symptoms had started in March, 1956, a week after an attack of pneumonia He had been a coalminer many years previously and had been a heavy smoker

On examination his general condition was poor His hands were swollen with œdema and showed severe clubbing (fig 1) Pain was particularly severe in his right hand, wrist and, elbow He had massive œdema of his ankles and feet with extreme tenderness Air entry was diminished over his left upper lobe, and numerous rhonchi were heard over his left lung He was dyspnœic on the slightest exertion and had marked bilateral gynæcomastia There were no other relevant findings

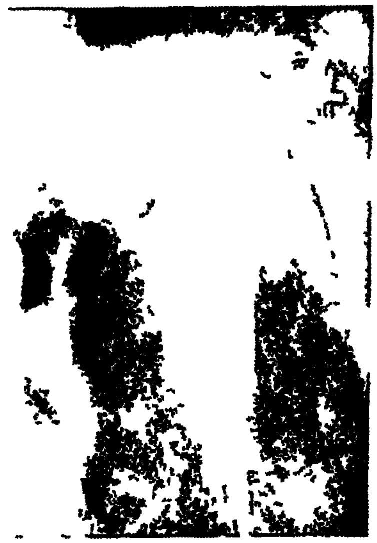

Fig 2—Case 1 tomograph showing rounded mass in upper lobe of left lung

Radiography of his chest showed a peripheral rounded opacity in the upper lobe of the left lung Tomography showed that this opacity was homogeneous and had rather ill-defined margins, suggesting a bronchial carcinoma (fig 2)

Bronchoscopy showed no abnormality Severe bronchitis contra-indicated resection

Treatment—Three days after admission, deep X-ray therapy was begun and a tumour dose of 3485r was given over thirty days In spite of this there was no improvement in the severe pain of the osteoarthropathy, the dyspnœa was not alleviated, and the patient remained completely bedridden Although his very poor condition made him a grave operative risk, it was thought justifiable to try the effect of vagotomy, without attempting to remove the tumour

Operation—A left lateral thoracotomy was done in June, 1956, by Mr J R Belcher The vagus nerve was identified and divided beneath the arch of the aorta immediately below the point where the recurrent laryngeal nerve was given off No other structures were disturbed

Postoperative course—Within twenty-four hours all the pains in the bones and joints were relieved, the swelling and œdema of the hands and feet were regressing, and the movements of the hands and fingers had much improved In three days the œdema had completely disappeared, the dyspnœa was considerably improved, and the patient got up At the end of ten days he was walking round the ward pain-free

Discharge and follow-up.—He was discharged from hospital on the thirteenth postoperative day On the twenty-fifth postoperative day he walked into the outpatients clinic without any pain, œdema, or gynæcomastia He was last seen nine months later, when he complained of considerable loss of weight and vomiting His general condition was deteriorating, and his liver was grossly enlarged, but he still had no pain or œdema, although the clubbing was still present He was not dyspnœic and had no gynæcomastia

Case 2.—A man, aged 57, was admitted in August, 1956, complaining of feeling unwell and of having lost weight since an attack of "influenza" in February Since May, 1956, he had noticed clubbing of his fingers and toes and had increasing painful swelling of his ankles and knees Mild dyspnœa had been present for the same period He had smoked heavily for forty years

On examination he had marked clubbing of his fingers and toes and swelling of his ankles and knees Movement of these joints was painful and limited

Radiography of his chest showed a large rounded mass in the right mid-zone, extending outwards to the chest wall in the axilla (fig 3)

Bronchoscopy showed a submucous infiltration of the lateral wall of the right main bronchus, and biopsy of this area disclosed a poorly differentiated carcinoma

Operation.—A right thoracotomy was done in August, 1956 by Mr J W Jackson A growth was found in the right upper lobe, extending across the oblique fissure but not adherent to the parietal pleura Large lymph-nodes involved by carcinoma in the hilum made the growth inoperable The vagus nerve was therefore identified above the hilum and divided

Postoperatively the relief of pain was immediate and the œdema disappeared within forty-eight hours On the thirteenth postoperative day a course of deep X-ray therapy to the primary tumour and to bilateral supraclavicular glands which had appeared since the operation, was begun A tumour dose of 2834r was given over three weeks The patient was discharged from hospital on Sept 24, 1956

Follow-up.—In January, 1957, he had a second palliative course of deep X-ray therapy to secondary deposits in his pelvic bones, ribs, and cervical lymph-nodes Despite progression of his metastases he had no further symptoms from his pulmonary osteroarthropathy There was no change in the degree of clubbing His general condition continued to deteriorate, and he died in March, 1957

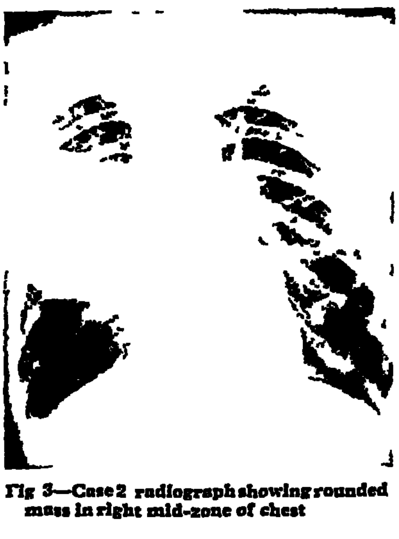

Fig 3—Case 2 radiograph showing rounded mass in right mid-zone of chest

Discussion

Both patients had severe pulmonary osteoarthropathy, of which pain was the prominent symptom This pain completely overshadowed the pulmonary symptoms of carcinoma

The rapid and complete relief of pain in the joints, followed by resolution of the swelling and œdema, confirm the finding of Flavell (1956) An unusual feature was the bilateral gynæcomastia in case 1, which regressed after vagotomy The association of gynæcomastia with carcinoma of the bronchus has been noted previously, Stephens (1928) reported an incidence of 7%, and Semple and McCluskie (1955) of 8 3% No case has hitherto been reported which had been successfully treated by vagotomy

Although the causation of osteoarthropathy is unknown, the nervous theory of Cudkowicz and Armstrong (1953) appears to be the soundest They postulate a pulmonary autonomic systemic vascular reflex by which ischæmia in parts of the lung distal to the tumour reflexly cause systemic arteriovenous anastomoses to open up in the limbs

In the present two cases the following points support the theory that hypertrophic pulmonary osteoarthropathy is primarily due to a nervous and not a chemical mechanism

(1) If osteoarthropathy were caused by a chemical substance liberated by the tumour, one would expect that the most severe manifestations would be associated with tumours with extensive secondary deposits Local removal of a small tumour, however, may give remarkable and usually permanent relief from osteoarthropathy It is uncommon for pain and swelling to occur after resection, even though extensive metastases develop later

(2) The associated gynæcomastia could be explained by the pulmonary autonomic systemic vascular reflex theory, arteriovenous anastomoses opening up in the breast as in the limbs

(3) Many lesions, totally different in ætiology and pathology, produce the manifestations of hypertrophic pulmonary osteoarthropathy A common autonomic pathway could be postulated for most of these, but would meet with many difficulties by a chemical or a hormonal explanation In the present cases simple division of the vagus produced relief of the pain and resolution of the œdema, although the pulmonary lesion was undisturbed (It might be objected that the deep X-ray therapy to the primary lesion might have had an effect, but this is extremely unlikely because in case 2 the beneficial effects of the vagotomy were clear before the X-ray therapy was started)

The complete relief of the pain and the disappearance of the œdema, despite the progression of the disease and the persistence of clubbing, appear, from the follow-up in these cases, to be permanent

Many patients with hypertrophic pulmonary osteoarthropathy associated with an inoperable carcinoma of the bronchus might receive much benefit from vagotomy (which might be done through a thoracoscope)

Probably all patients undergoing thoracotomy for inoperable carcinoma of the bronchus, should also undergo routine vagotomy on the side of the lesion, irrespective of whether they have osteoarthropathy at the time or not

In this way patients who have, or may have, one of the most painful manifestations of carcinoma of the bronchus may be saved a great deal of pain and discomfort and will therefore be able to spend several months of active life

Summary

Two patients with inoperable pulmonary carcinoma and severe hypertrophic pulmonary osteoarthropathy treated by vagotomy obtained immediate complete relief of disabling pain Associated œdema and, in one case, gynæcomastia also disappeared

The possible mechanism of hypertrophic pulmonary osteoarthropathy is discussed, and a nervous reflex is favoured

Despite the fact that this condition is rare, patients who undergo thoracotomy for an unresectable carcinoma of

the bronchus should have a vagotomy on the side of the lesion done as a routine In inoperable cases with hypertrophic pulmonary osteoarthropathy this should be done where possible By this relatively minor operation these patients will not only be saved much pain and misery but will also possibly live many months of active life

We are grateful to Prof B W Windeyer, Mr T Holmes Sellors, Miss M D Snelling, Mr J R Belcher, and Dr A M Jelliffe for permission to publish these cases, and we wish to thank Mr M. Turney and the staff of the photographic department of the Middlesex Hospital for their invaluable help with the illustrations

REFERENCES

Avarez, G H. (1948) *Rev Asoc. med argent* 62, 690
Brea, M M. (1948) cited in The Year Book of General Surgery (edited by E A Graham), p 306 Chicago
Cudkowicz, L., Armstrong, J B (1953) *Brit J Tuberc.* 47, 227
Flavell, G (1956) *Lancet*, i, 260
Hansen, J L (1954) *Int Congr Dis Chest*
Lumb, W V, Carlson, W D (1956) *J Amer vet med.Ass* 128, 185
Mendlowitz, M (1942) *Medicine, Baltimore*, 21, 269
Semple, T, McCluskie, R. A. (1955) *Brit med J* i, 754
Stephens, B P (1928) unpublished thesis, Mayo Clinic Foundation.
Wyburn-Mason, R. (1948) *Lancet*, i, 203

PENICILLIN SENSITIVITY IN PATIENTS WITH BURNS

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WITHIN recent years there have been a number of deaths from penicillin therapy (Wilensky 1946, Waldbott 1949 *British Medical Journal* 1951, Thompson 1952, Harpman 1952, Kern and Wimberley 1953, Feinberg and Feinberg 1956) and an increase in sensitivity reactions (*Lancet* 1957) The reported incidence has varied from 1 2% (Lepper et al 1949) to 60 5% (Cormia et al 1945), but 5–6% seems to be the usual reaction-rate following intramuscular injection (Mayer et al 1953, Feinberg and Feinberg 1956) Detailed reports of reactions following local application of penicillin are few, but Kern and Wimberley (1953) stated that it leads to sensitivity more commonly than any other mode of administration, and figures of 10–20% have been cited (Templeton et al 1947) By contrast, Collier (1958) found no sensitivity reactions in about 11,000 minor burns and wounds treated with penicillin ointment.

Penicillin cream has been used as the routine treatment for burns at the Birmingham Accident Hospital since 1945 It was introduced as a result of the observation in Glasgow that penicillin cream was efficacious against hæmolytic streptococcal infection of burns (Clark et al 1943), and it has been proved to have considerable prophylactic value against the same organism (Jackson et al 1951)

In the past, sensitivity reactions to local penicillin in this unit have been few and transient (Bull et al 1954), but, in view of the reported increasing incidence of sensitivity reactions, the risks involved in the continued use of local penicillin have been freshly assessed

Method

All patients were reviewed who attended the burns unit for the first time between Jan 1 and June 30, 1957 The clinical staff were informed of the intended survey and recorded any possible allergic reaction The use of 1% cetrimide as a cleansing agent was discontinued for the period of the review, since it can also cause sensitivity

Penicillin cream was made in the following base

Ol ricini	28%
'Lanette Wax S.X.'	14%
Glycerin	10%
Aqu. ad	100

TABLE I—FORMS OF PENICILLIN TREATMENT

Form	Inpatients	Outpatients	Total
Cream	82	1046	1128
Powder	49	266	315
Spray	25	10	35
Jelly	0	8	8
Eye ointment	1	1	2
Oral	7	6	13
Intramuscular	15	26	41
No receiving more than one form	59	197	256
Total	120	1166	1286

The usual concentration of penicillin was 1000 units per g, but some patients had 10,000 units per g for treatment of streptococcal infection Penicillin powder was made up in a lactose powder base (10,000 units per g)

1419 new patients attended during the six-month period. Of these, 1260 were outpatients, 135 were inpatients, and 24 were treated initially as outpatients and were admitted later This last group has been included with the outpatients, since most of the penicillin cream was applied before admission 436 outpatients (34%) and 68 inpatients (50%) were under 14 years of age.

1286 patients received penicillin during treatment, most of them having it locally (table I)

Results

Reactions

No anaphylactic reaction occurred In 35 cases a rash developed In some patients this was obviously due to a cause other than penicillin (for example, measles), but in 10 patients it was considered on clinical grounds that the rash might be a penicillin sensitivity reaction (table II) Other possible sensitising agents had been given to four of these patients—namely, plasma (3), blood (1), streptomycin (1), and a jelly of unknown composition (1) 4 of the reactions followed the systemic administration of penicillin (3 intramuscularly, 1 orally) combined with local therapy. In the majority the rash occurred twelve to sixteen days after burning, in 3 it occurred on the fourth to fifth days, and in the remaining patient on the twenty-second day a few hours after the first injection of penicillin No rash lasted longer than four days, and in the majority it subsided within forty-eight hours 6 of the 10 patients had penicillin cream applied again, three days to six months later, with no reaction

Only 1 patient had any systemic upset accompanying the rash

This patient sustained an 8% burn of face and hands The hands were dressed with penicillin cream and the face was treated by exposure with penicillin powder The dressings were changed on days 1, 4, 11, and 14 On the evening of day 14 an urticarial rash developed on the legs and trunk. The patient was given mepyramine 100 mg t.d s, and calamine lotion was applied locally The following day the rash continued, she complained of abdominal pain and vomited twice On day 16 the dressing was changed to tulle-gras, and the rash faded. Skin-grafting was carried out on day 19 and tulle-gras dressings were continued. On day 31, group-A hæmolytic streptococci were found on the hands, which were then dressed with penicillin cream 10,000 units per g This dressing was repeated on days 32, 34, 36, 37, 39, and 40 There was no reaction to these later applications

2 other patients had a definite allergic reaction, but as neither had received penicillin in any form the reaction could not be attributed to this cause

If the rashes have been correctly attributed, then the total incidence of penicillin reactions was 0 8% (10 out of 1286) The incidence in inpatients was higher (3 3%) than in outpatients (0 5%) Although this could be due to more extensive application of the cream, it seems more

TABLE II—RASHES IN 1419 PATIENTS

Type of reaction	Inpatients	Outpatients	Cause to which rash attributed				No penicillin before rash	"Penicillin" rash, no reaction to later penicillin
			Penicillin	Infection	Irritation	Other		
Urticarial with systemic upset	1	0	1					1
Urticarial only	3	1	4					3
Measles	4	0		4				
Chickenpox	1	0		1				
Scarlatinaform with hæmolytic streptococcal infection	2	1		3			1	
Generalised erythematous (other than above)	2	5	4	1		2*	2	2
Localised	3	12	1	4	10		2	
Total	16	19	10	13	10	2	5	6

* 1, tulle-gras, 1, blood-transfusion

likely to be the effect of a larger number receiving systemic therapy The overall incidence of reactions in those receiving local application only was 0 5% (6 out of 1232), and in those having systemic therapy, usually combined with local, 7 4% (4 out of 54)

Since a number of outpatients had minor burns and did not attend hospital more than once or twice, these figures may be falsely low 203 outpatients receiving penicillin were transferred, or did not attend more than twice If, for this reason, these patients are excluded, then the total incidence of reactions was 0 9% (10 out of 1083), in outpatients 0 6% (6 out of 963), from local application only 0 6% (6 out of 1030), from combined systemic and local administration 7 6% (4 out of 53)

History of Previous Sensitivity

14 outpatients (1 1%) and 3 inpatients (2 2%) gave a history of allergy to penicillin 7 of these had penicillin cream applied during treatment, and none had a reaction

One patient with a history of penicillin sensitivity had a reaction

This patient had penicillin injections on account of a septic finger in 1955 Eighteen months later (December, 1956) he sustained a 1 5% burn of the forearm, which was treated with penicillin powder and boracic fomentations at work When he was referred here two weeks after injury, the area was rather swollen Penicillin cream was applied, and three days later he had a sensitivity reaction The dressing was changed to tulle-gras, but he returned the following day with the arm more swollen and painful, and a vesicular eruption over the whole burned area The reaction gradually subsided with local calamine lotion and systemic antazoline In June, 1957, he sustained a small burn of the opposite forearm This was dressed with tulle-gras, and two days later he returned with swelling of the forearm and a vesicular rash over the area covered with tulle-gras The rash and burn healed in two weeks It is apparent that this patient was sensitive to tulle-gras which he had on both occasions, as well as to penicillin

Discussion

In assessing the incidence of penicillin sensitivity, the first difficulty is correct diagnosis Where patients are exposed to several possible sensitising agents, this may be extremely difficult Skin tests are generally considered to be unreliable (Farmer 1953, Tuft et al 1955, Feinberg and Feinberg 1956) and penicillin sensitivity may be lost spontaneously (Matthews et al 1956) 6 of our patients with "penicillin sensitivity" had no reaction to repeat applications within six months, either they must have lost their sensitivity very rapidly, or the reaction was wrongly attributed to penicillin Similarly, of the 17 patients who gave a history of previous allergy, 7 were exposed to the drug with no reaction

None of the reactions in these patients endangered life, nor are we aware of any serious reaction during the thirteen years the drug has been used routinely here Most of the reactions were mild and transient, and some would not have been noted had the review not been in progress Only a few patients had any appreciable discomfort from the reaction

Comparing the incidence of reactions in this series with other published results, the reaction-rate after systemic administration (7 4%) is of a similar order to that found by other workers (Lyons 1943, 5 7%, Mayer et al 1953, 6%, Vickers et al 1958, 5%) Our incidence after local application only (0 5%) is much lower than other reported figures Reports of reaction to local therapy have usually been on patients with dermatitis, who are probably particularly susceptible (Kolodny and Denhoff 1946) The present results, in patients without skin disease, show a very low reaction-rate to local application of penicillin, and much lower than to systemic administration

The necessity of incurring even this small risk may reasonably be questioned, and there would be no justification if there was another agent which was as effective and safer Local penicillin cream is at present the best prophylactic agent against colonisation with *Streptococcus pyogenes*, which so frequently causes graft failure In a controlled trial of cases of burns, *Str pyogenes* infection developed in only 3 7% of cases treated with penicillin cream, compared with 47 4% in a control group (Jackson et al 1951) In view of its obvious advantages and the low incidence of reactions penicillin cream can justifiably be applied prophylactically

Summary

1419 patients with burns were observed for evidence of any sensitivity reaction

0 5% (6 out of 1232) of patients receiving local penicillin had a reaction possibly attributable to penicillin, compared with 7 4% (4 out of 54) of patients receiving systemic penicillin Most of the reactions were mild, and none lasted longer than four days

Accurate diagnosis is often difficult, and the sensitive state may be transient, as is illustrated by the fact that 6 of the 10 patients with "penicillin sensitivity" had no reaction to subsequent local application of the drug

REFERENCES

British Medical Journal (1951) i, 1269
Bull, J P, Jackson, D M, Lowbury, E J L, Topley, E (1954) *Lancet*, i, 161
Clark, A M, Colebrook, L, Gibson, T, Thomson, M L, Foster, A (1943) *Lancet*, i, 605
Collier, E (1958) *Brit med J* i, 396
Cormia, F E, Jacobsen, L G, Smith, E L (1945) *Bull U S Army med Dept* 4, 694
Farmer, P W (1953) *Med J Aust* ii, 820
Feinberg, S M, Feinberg, A R (1956) *J Amer med Ass* 160, 778
Harpman, J A (1952) *Brit med J* ii, 392
Jackson, D M, Lowbury, E J L, Topley, E (1951) *Lancet*, ii, 705
Kern, R A, Wimberley, N A (1953) *Amer J med Sci* 226, 357
Kolodny, M H, Denhoff, E (1946) *J Amer med Ass* 130, 1058
Lancet (1957) ii, 929
Lepper, M H, Dowling, H F, Robinson, J A, Stone, T E, Brickhouse, R L, Caldwell, E R, Whetton, R L (1949) *J clin Invest* 28, 826

references continued at foot of next column

ANXIETY STATES FOLLOWING VESTIBULAR DISORDERS

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DISTURBANCES of balance resulting from vestibular disorders have long been known to lead to severe anxiety (Gowers 1893, Cawthorne 1957) The recent finer analysis of affections of the eighth nerve, in particular by Hallpike and his colleagues (Cawthorne et al 1956, Carmichael et al 1956), has led to improved diagnosis of these patients The factor of positional nystagmus of the benign paroxysmal type in causing some of the symptoms of the post-traumatic state has been emphasised (Gordon 1954, Harrison 1956), together with the importance of differentiating these symptoms from those of psychological origin Less attention has been paid to the mental features displayed by patients with disturbances of balance

On the other hand, complaints of disturbance of balance are a classical feature of hysteria and anxiety states (Mayer-Gross et al 1954) and are then generally accepted as being without organic basis We review here 12 cases (see table) in which anxiety states followed directly on disturbance of balance and the symptoms attributable to anxiety predominated The prognosis of these anxiety states appeared to depend on the recognition and treatment of the primary disturbance.

Illustrative Case-reports

Case 1 —A clerk and housewife, aged 24, developed attacks of unsteadiness, feeling " as if mildly drunk " and as if she had just been subjected to rotation, brief initially but later more persistent, and increasingly accompanied by panic attacks, depression, fears of dying, and a feeling of vibration in the head with preoccupation about her symptoms (She had no rotatory vertigo until six months after the onset.) She had previously been free from neurotic symptoms, apart from a tendency to worry When seen five weeks after the onset caloric responses were minimal No diagnosis, however, could be made by otological examination. She improved slowly at first with sedation and reassurance, and more rapidly when she was instructed in a range of balancing exercises seven weeks after the onset She returned to work six weeks later, and her symptoms continued to improve When seen six months after the onset her caloric responses showed no change, she reported that this test led to rotatory vertigo followed by her non-rotatory unsteadiness A year after the onset she had been symptom-free for five months

Case 3.—A male factory worker, aged 43, had had occasional attacks of vertigo lasting up to five minutes since the age of 12 years He had rotatory vertigo if the attacks came on when he was lying down, but in the erect position his surroundings seemed to tip to the right Of late he had become increasingly fearful of an attack, was never at ease sitting in a cinema even when at the back in the end seat, and felt particularly tense in the barber's chair In addition, apart from his attacks, for a month or so he would feel that he must walk on the left side of the pavement, and used to sweat if he had to walk on the right side He was adopted, had an unhappy childhood, walked once in his sleep, wet the bed until the age of 6 years, and occasionally stammered when flustered His caloric responses were normal but reproduced the sensation of vertigo No otological diagnosis was made He had not improved on anticonvulsants, but improved promptly when he was instructed in a range of balancing exercises His attacks of vertigo became somewhat less frequent, his feelings of anxiety vanished, and he reported that he was still well in this respect a year later

Case 12 —A housewife and hairdresser, aged 38, reported that, nine months previously, after a period of overwork, she developed a muzzy feeling with continuous headaches and depression, and three months later spent three weeks in bed feeling exhausted, during this time she had a continuous feeling that she was falling through the bed. She had previously been free from neurotic symptoms She continued to be depressed and to have dizziness and nausea, and did not improved with sedation and superficial psychotherapy Seven months after her first attendance she reported an attack in which her surroundings went round and round and she staggered, she then recalled that she had had this sensation fifteen months before her first attendance and earlier than that for very brief periods On otological examination her caloric responses were normal, apart from a minimal response to water at 44°C in the right ear, but she reported that the sensation she had experienced during irrigation was similar to her spontaneous dizziness and nausea No otological diagnosis was made She was then given bending exercises and promethazine chlorotheophyllinate (' Avomine ') 25 mg t.i d and reported an immediate improvement in her dizziness, maintained during follow-up

Symptoms

Of the 12 patients 8 (see table) had episodes of frank rotatory vertigo, usually of brief duration Case 5 had paroxysmal nystagmus of the benign positional type

Non-vertiginous symptoms attributable to vestibular disorder occurred in 9 patients and were described variously as giddiness, dizziness, unsteadiness, or impairment of balance In 5 patients (cases 4, 6, 8, 10, and 12) these symptoms were worse on movement, in case 2 after getting off a bus or a train, and in case 9 only during rapid movement of the head

Of the psychological symptoms the most common were panic attacks (7 patients), fears of travelling (5 patients), reactive depression (5 patients), feelings of tension (3 patients, in 2 of whom it was particularly severe in the barber's chair), and exhaustion (2 patients)

Treatment

An explanation that the primary disorder is an organic affection of the balancing mechanism often affords great relief to the patient, who may have been fearing insanity or a grave organic disorder Balancing exercises not only give confidence but also appear to hasten the disappearance of feelings of unsteadiness Three forms of balancing exercise were given, the simplest (cases 4, 5, 7, 11, and 12) being putting the head between the knees from a standing position ten times in succession, to be repeated several times a day (" bending exercises ") A full range of balancing exercises, from eye and head movements to vigorous bending (Cawthorne 1946, Cooksey 1946), was given to some of the patients, and was continued either at home (by cases 1, 3, 9, and 10) or in the physiotherapy department (by cases 2, 6, and 8) The simple bending exercises may suffice, but better results were obtained with the full range of balancing exercises Sedatives by day or night

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DR. DAVIES REFERENCES—*continued*

Lyons, C (1943) *J Amer med Ass* 123, 1007
Matthews, K. P , Hemphill, F M., Lovell, R G , Forsythe, W E., Sheldon, J M (1956) *J Allergy*, 27, 1
Mayer, P S , Mosko, M M , Schutz, P J Osterman, F A , Steen, L H., Baker, L. A (1953) *J Amer med Ass* 151, 351
Templeton, H J, Lunsford, C. J , Allington, H. V (1947) *Arch. Derm Syph* 56 325
Thompson, W O (1952) *Brit med J* ii, 70
Tuft, L., Gregory, D C., Gregory, J (1955) *Amer J med Sci* 230, 370
Vickers, H R., Bagratuni, L., Alexander, S (1958) *Lancet*, i, 351
Waldbott, G L., (1949) *J Amer med Ass* 139, 526.
Wilensky, A O (1946) *ibid* 131, 1384

ANALYSIS OF CASES

Case no	Sex	Age (yr)	Duration vestibular disorder (yr)	Rotatory vertigo	Non-rotatory vestibular symptoms	Reproduction of vertigo (V) or non-rotatory vestibular symptoms (I) by caloric test	Anxiety symptoms		Previous neurosis (severity 0–3)	Duration of follow-up after first being seen (yr)	Progress after treatment
							Severity (1–4)	Duration (yr)			
1	F	24	1/12	Late	+	V+1	4	1/12	1	1	Recovered
2	M	52	11	−	+	1	4	6	1	2 1/2	"
3	M	43	31	+	−	V	2	5	1	1	"
4	M	43	8/12	−	+	−	4	8/12	2	3/12	Improved
5	F	57	27	+	+	V	4	27	1	11/12	"
6	M	28	7	+	+	−	4	2	1	2	Recovered
7	F	26	9/12	+	−	−	2	6/12	0	5/12	"
8	F	16	6/12	−	+	?	4	9/12	3	6/12	I S Q
9	M	40	2	+	+	V	1	8/12	1	1 3/12	Recovered
10	F	28	6/12	−	+	1	4	3/12	0	7/12	Improved
11	F	25	1 6/12	+	−	V	3	1 6/12	0	1	I S Q
12	F	38	1 5/12	+	+	1	3	9/12	0	9/12	Improved

were given when they seemed required, but cases 7 and 9 recovered when bending exercises were introduced and sedatives stopped Antihistaminics were given to 5 patients (dimenhydrinate 50 mg t i d in cases 4, 5, 10, and 11, and promethazine chlorotheophyllinate 25 mg t i d in case 12) at the same time as exercises, and any independent effect they may have had could not be determined

Discussion

Vertigo has long been known to cause anxiety and the fear of further attacks On the other hand, complaints of unsteadiness, subjective and objective, are a classical feature of anxiety states and hysteria The present patients were all considered to have a vestibular disorder, 4 without rotatory vertigo and 3 without symptoms of unbalance between their attacks of vertigo In all the patients the outstanding and disabling symptoms were attributable to anxiety consequent on the vestibular disorder Usually those without previous neurotic traits were less severely affected as regards their anxiety symptoms, as would be expected, but their outcome was no better Absence of rotatory vertigo was an unfavourable prognostic symptom 3 patients (cases 2, 5, and 12) had had long periods of psychiatric treatment without any improvement until the organic basis of their disability was recognised The response to treatment by explanation and exercises was encouraging, 6 patients becoming free from anxiety, and 4 others showing definite improvement

From the otologist's point of view these cases present considerable difficulty The tests for vestibular disturbance are still relatively undeveloped, and while the differential caloric test of Fitzgerald and Hallpike (1942) is most helpful it cannot provide conclusive evidence in every case The difficulties of the test are well known the test needs an expert to apply it, and the margin of error of the test should lead to reserve about its interpretation in the absence of other signs In vestibular neuronitis there may be a complete lack of vestibular response on one side, whereas the other may be normal, and in this event a diagnosis can be made with certainty On the other hand, the equally well-known condition of benign paroxysmal nystagmus, when transient vertigo develops with the head in certain positions, may be associated with a normal response to the differential caloric test In benign paroxysmal nystagmus the signs may wax and wane, so that a patient may have this disease and yet, if his visit to hospital coincides with a period of freedom, may show no sign to the examiner The possibility, therefore, that a patient with this disorder may be thought to be entirely neurotic should make for hesitation in assessing a patient who is described as a victim of vertigo These patients should certainly be examined as thoroughly as possible, and it is a reasonable suggestion that no one who can complain in detail of an apparent movement of objects should be considered neurotic Whether this complaint can be confirmed by objective evidence is uncertain, it clearly can sometimes, but there is often doubt because the available vestibular tests are not sufficiently accurate That a patient with an established disorder—such as Ménière's disease—can develop a neurosis is equally well known All otologists will know of patients with Ménière's disease who were considered to be neurotic, simply because the neurosis which had developed was so obvious that it concealed the Ménière's disease There is no reason why this should not happen in other vestibular disorders, and in future more precise methods of examination may supply proof of organic disease in patients who would otherwise be considered neurotic

The caloric responses of the present patients cannot be attributed to anxiety, because they differ from those found by Hallpike et al (1951) in 35 patients with severe anxiety neurosis, who showed greater overall sensitivity with a greater degree of variance than did a healthy group

Our patients were extracted from 466 consecutive patients without organic disease of the central nervous system referred to one of us (R T C P) for psychiatric opinion by the physicians of the neurological hospital over a period of three years Thus the syndrome appears to be common, although it may be over-represented in the material of a neurological hospital

The association between vertigo and endogenous depression is also of interest Of 146 patients with endogenous depression seen over the past three years at this hospital, in 14 a complaint of vertigo was made and was considered to have a basis in an organic vestibular disorder In 10 of these patients the attacks of vertigo and of depression were independent, in 3 the onset of vertigo led directly to a recurrence of a depressive state, and in 1 the onset of vertigo led to the initial attack of endogenous depression It is therefore possible that vestibular disorders may be counted among those physical illnesses incriminated by Roth and Kay (1956) as responsible in some patients for the precipitation of an attack of endogenous depression

Summary

An account is given of 12 patients in whom anxiety states directly followed disturbances of balance and in whom the symptoms attributable to anxiety predominated

The prognosis of these anxiety states depended largely

on recognition of the primary disorder and on treatment by balancing exercises.

We wish to thank our colleagues at Maida Vale Hospital for referring these patients to us, and Dr. Eliot Slater and Dr. Alick Elithorn for their advice and criticism.

REFERENCES

Carmichael, E. A., Dix, M. R., Hallpike, C. S. (1956) *Brit. med. Bull.* 12, 146.
Cawthorne, T. (1946) *Proc. R. Soc. Med.* 39, 270.
— (1957) *Med. Pr.* 237, 560.
— Dix, M. R., Hallpike, C. S., Hood, J. D. (1956) *Brit. med. Bull.* 12, 131.
Cooksey, F. (1946) *Proc. R. Soc. Med.* 39, 273.
FitzGerald, G., Hallpike, C. S. (1942) *Brain*, 65, 115.
Gordon, N. (1954) *Lancet*, i, 1216.
Gowers, W. R. (1893) A Manual of Diseases of the Nervous System, vol. II, p. 788. London.
Hallpike, C. S., Harrison, M. S., Slater, E. (1951) *Acta oto-laryng., Stockh.* 39, 151.
Harrison, M. S. (1956) *Brain*, 79, 474.
Mayer-Gross, W., Slater, E., Roth, M. (1954) Clinical Psychiatry, pp. 121, 131. London.
Roth, M., Kay, D. W. K. (1956) *J. ment. Sci.* 102, 141.

ACUTE RENAL FAILURE DUE TO MUSCLE NECROSIS IN CARBON-MONOXIDE POISONING

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SKELETAL muscle necrosis leading to acute tubular necrosis of the kidneys is a rare complication of carbon-monoxide intoxication.

Günther (1921) recorded fatal renal damage, with oliguria, in an adult male following eleven hours' coma due to exposure to carbon monoxide in a cold atmosphere; an abnormal pigment, described as hæmatoporphyrin, was found in the urine. The necropsy findings in the same case (Scharmann 1921) revealed degeneration of the muscles in the areas affected by postural pressure.

Hedinger (1948) reviewed 30 cases of muscle necrosis in carbon-monoxide poisoning; the affected muscles were painful and swollen, and in 12 cases histological confirmation was obtained.

In Fowler's (1954) case of gangrene in a lower limb, following carbon-monoxide poisoning, peripheral vascular disease was probably an important factor. The patient, a man aged 58, had a previous history of intermittent claudication, and his femoral artery, on amputation, showed gross atheroma with medial calcification. No reference was made to renal lesions in this case.

Mautner (1955) described a case of attempted suicide with carbon monoxide, in which temporary oliguria with a non-protein-nitrogen level of 85 mg. per 100 ml. was associated with brawny œdema of the right shoulder, upper arm, and thorax, and muscle necrosis was found on biopsy. Mautner credits Larrey (1812) with the first description of muscle necrosis in carbon-monoxide poisoning. Probably, however, the sacral and scapular lesions were superficial pressure sores rather than areas of muscle necrosis. There was no reference to renal lesions in these cases.

The present paper records the clinical and pathological findings in a fatal case of acute tubular necrosis of the kidneys following myonecrosis in coal-gas poisoning, and emphasises the importance of frequent clinical and laboratory assessment of such cases in view of the particular biochemical hazards in renal failure from this cause.

Case-report

A female Indian student, aged 23, was found unconscious in a gas-filled room on Sept. 24, 1957. On admission to hospital an hour later she had recovered consciousness but complained of pain in her back and in both legs.

On examination she was an obese girl of healthy appearance, who made no spontaneous movements of either leg and had a variable degree of hypoæsthesia to pinprick. Direct questioning revealed no history of suicidal intent, the accident having occurred through ignorance of the mechanism of gas-heating. She had probably been unconscious for at least seven hours, and the position of her lower limbs on discovery suggested an initial squatting posture.

Progress.—Next day she vomited several times and passed less urine (not accurately recorded). Within the next twenty-four hours she passed only 180 ml. of urine, and on Sept. 27 her blood-urea level had risen to 163 mg. per 100 ml. Her blood-pressure was 115/80 mm. Hg, and she had no anæmia. Gynæcological examination revealed no abnormality. No past history of renal disease, diabetes, or exposure to known renal toxins was obtained. Catheterisation of the bladder on Sept. 28 produced 90 ml. of urine with Sp. gr. 1·016 and moderate proteinuria but no glycosuria. Conservative treatment of acute renal failure was instituted with hypertonic dextrose solution administered through a polyethylene catheter into the superior vena cava.

On Sept. 30 an extensive soft-tissue swelling, with œdema of the overlying skin, was observed to involve the inner side of the right thigh and to extend above the inguinal ligament. There was extreme local tenderness but no superficial bruising. Limitation of internal rotation at the right hip-joint was present, and the limb was held in a position of external rotation. There was, however, no shortening of the leg. Tendon-reflexes were absent on the right side, and neither plantar response could be elicited. Appreciation of pinprick was impaired, but a segmental distribution could not be defined.

At this stage, six days after the onset of oliguria, acidotic breathing was noted, though the patient remained fully conscious, with blood-pressure 120/85 mm. Hg, optic fundi normal, and both kidneys enlarged and tender. The blood-urea level had risen to 325 mg. per 100 ml. and the serum-potassium level to 5·9 mEq per litre. Electrocardiography showed minimal peaking of T waves in precordial leads. There was a significant acidæmia, with serum-bicarbonate level 16·9 mEq per litre. The hæmoglobin level was 13·9 g. per 100 ml., white blood cells numbered 4000 per c.mm., and the erythrocyte-sedimentation rate was 12 mm. in the first hour (Westergren). Radiography of the lumbosacral spine and hip-joints was normal.

On Oct. 1 the patient passed only 90 ml. of urine. Her blood-urea level was 335 mg. per 100 ml., serum-potassium level 6·8 mEq per litre, and serum-bicarbonate level 12·8 mEq per litre. Soluble insulin was added to the intravenous infusion, and an attempt was made to give ion-exchange resin by mouth though vomiting was still frequent. On Oct. 2, although the blood-urea level had risen to 470 mg. per 100 ml., the patient's general condition was satisfactory and vomiting less troublesome. There was no impairment of consciousness, and she could now move the affected leg, which, however, was still swollen. Her serum-bicarbonate level remained at 12·7 mEq per litre, and her serum-potassium level was 7·0 mEq per litre. Preparations for hæmodialysis with an artificial kidney were being made, when the patient collapsed suddenly at 6 A.M. on Oct. 3 with impalpable pulse and unrecordable blood-pressure and died within a few minutes.

Necropsy findings.—The body was that of a well-built obese young Indian woman. The upper third of the right thigh appeared swollen, and incisions into it revealed œdema of the subcutaneous tissues The underlying adductor-muscle group, for about twelve inches of its length, was abnormally pale, yellowish-grey, and patchily mottled Some areas presented a “ fish-flesh ” appearance The muscles of the other limbs showed no abnormality The meninges and cerebral hemispheres were congested, and the brain was œdematous The heart was normal in size, with healthy valves, coronary arteries, and aorta There were bilateral terminal congestive changes in the lungs, with a normal pulmonary arterial tree Acute congestion of the liver was present The kidneys were pale and swollen, weighing 210 and 220 g The tense capsule stripped readily from the renal substance, and the cortex was pale, moist, and increased in width The medulla was mottled dusky red, and its junction with the cortex was indistinct There was no occlusion of the renal vessels The uterus and adnexa appeared healthy

Histology —Sections from the affected muscle revealed changes varying from loss of striation to complete degeneration of fibres (fig 1) Most fibres appeared waxy, with fragmentation, vacuolation, and shrinkage of degenerate sarcoplasmic remnants In some areas phagocytosis of dead muscle by histiocytes was seen, while elsewhere empty sarcolemmal sheaths were evident Areas of hæmorrhage between the muscle bundles were prominent in one section There was interstitial œdema with invasion by polymorphs, eosinophils, and lymphocytes No calcification was seen Many arterioles showed fibrinoid necrosis with intraluminal thrombi in some instances There was much perivascular cuffing with polymorphs and mononuclear cells There was no abnormality of the larger vessels Sections of the kidneys revealed glomeruli which were normal apart from an eosinophil coagulum in some of the capsular spaces (fig 2) The distal convoluted and collecting tubules contained dense benzidine-positive casts Some of the proximal tubules were intact, but others were dilated and lined by flattened regenerating epithelium There was some œdema of the interstitial tissue, with infiltration by chronic inflammatory cells, and in the cortex there was evidence of a focal perivascular histiocytic reaction adjacent to ruptured tubules Sections of blood-vessels from other organs in the body showed no abnormality.

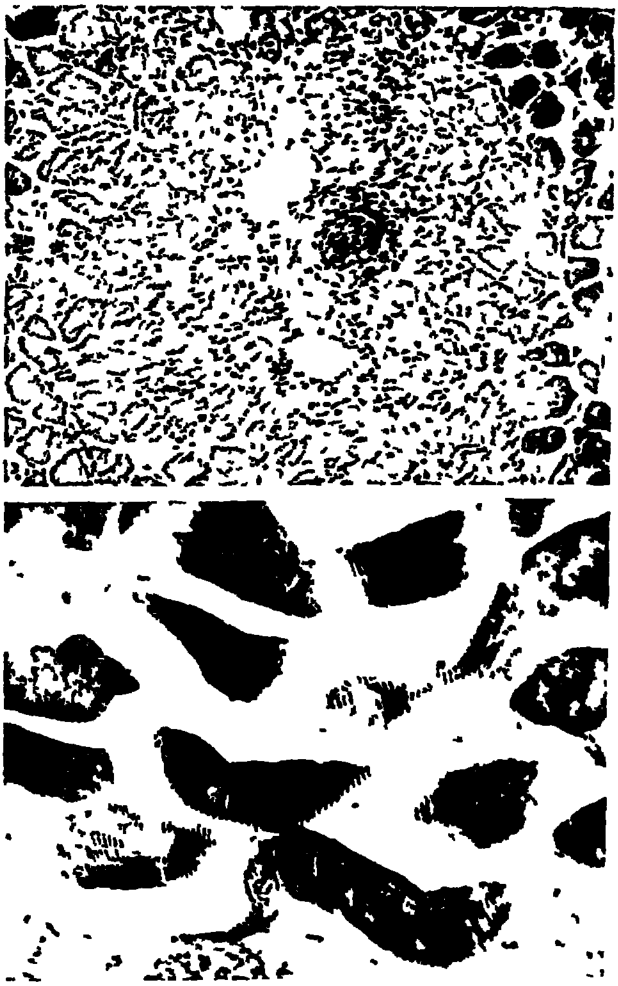

Fig 1—Section of adductor muscle showing upper part, disruption of fibres, arterial necrosis, and cellular infiltration (hæmatoxylin and eosin, ×93), lower part, loss of striation (phosphotungstic acid hæmatoxylin, ×177)

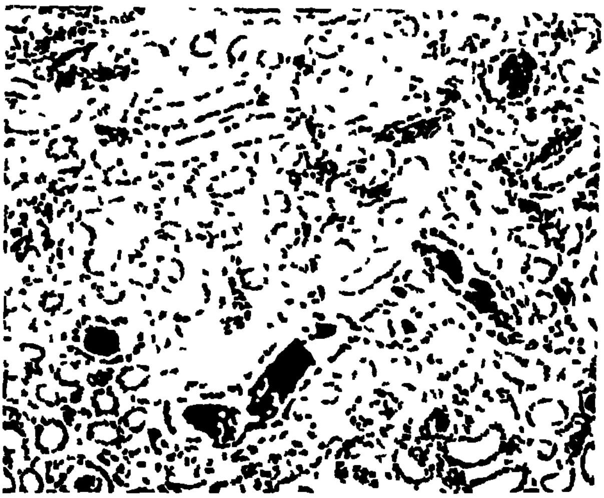

Fig 2—Section of kidney showing tubular casts and regenerating epithelium (hæmatoxylin and eosin, ×158)

Discussion

The association of myoglobinuria with acute tubular necrosis of the kidneys is well recognised Myoglobinuria results from damage to skeletal muscles, of which the main causes, in man, are trauma and Haff disease (Hed 1955) The latter condition, believed by some to be a seafood allergy, has been reported mainly in East Prussia Other non-traumatic causes, listed, by Hed, include arterial occlusion with ischæmia, convulsions, myositis, muscular dystrophy, and paroxysmal myoglobinuria without progressive muscular dystrophy The traumatic group comprises crush injuries, high-voltage shocks, and localised muscle necrosis due to postural pressure

In the present case muscle necrosis followed seven hours’ exposure to carbon monoxide, with presumed immobilisation of the patient, and was restricted to a localised area of one leg Probably the combined factors of local ischæmia due to pressure, particularly in an obese person, and anoxæmia, due to carbon monoxide, were responsible for the muscle damage The importance of decreased arterial oxygen, due to carbon monoxide, has been emphasised, perhaps in such cases the gas interferes directly with the oxidative enzymes of muscle by forming carboxymyoglobin Histologically there was no evidence of generalised arterial disease, sections of vessels from other organs being quite normal

Pressure necrosis of muscle has been reported to follow unconsciousness due to other agents, including alcoholism, alcoholism plus “ sleeping tablets ” (Jasinski and Brutsch 1952), barbiturates (Touzé and Thierry 1952), alcoholism plus barbiturates (Fahlgren et al 1957), and general anæsthesia (Gordon and Newman 1953) In some of the published cases the patients were obese, and the assumption of an abnormal posture during immobilisation has been emphasised

Most of the published cases of muscle necrosis following prolonged coma have been followed by acute renal failure In some such cases myoglobin pigment was found in the urine during life, whereas in others pigment casts in the renal tubules were found at necropsy In the present case myoglobinuria was not found, but the typical casts were present in the kidneys The histological findings were those of acute tubular necrosis, the large numbers of casts in the collecting tubules, some interstitial reaction, polymorph invasion of casts in the cortical zone, and evidence of regeneration of tubular epithelium being consistent with a duration of ten days There was no evidence of antecedent renal disease.

Early recognition of renal involvement in cases of muscle necrosis is important for the institution of a suitable regime for treating acute tubular necrosis of the kidneys Exact diagnosis depends on the spectroscopic demonstration of myoglobin in the urine, but, since this is early and probably transient, it is unlikely to be found at the stage of clinical renal failure. It is important to exclude muscle necrosis in patients developing acute renal failure after coma, particularly where it is associated with anoxæmia. A suspected clinical diagnosis can be confirmed or refuted by muscle biopsy

The renal lesion associated with muscle necrosis is potentially reversible, but the biochemical hazards, in particular that of sudden hyperkalæmia, seem less predictable than in tubular necrosis from other causes—e g ischæmic "shock" and drugs Of Fahlgren's (1957) 5 patients with myonecrosis and myoglobinuria following alcohol and barbiturate poisoning 2 died from hyperkalæmia. Hed's (1955) patient with renal failure, following the allied idiopathic condition of paroxysmal myoglobinuria, died with a serum-potassium level of 12 3 m.Eq per litre and gross electrocardiographic evidence of hyperkalæmia In the present fatal case the cause of death was presumed to be a further sudden rise in serum-potassium level above the last recorded figure of 7 0 m Eq per litre It is imperative, therefore, that such cases should have at least twice-daily estimations of serum electrolyte levels, particularly potassium, and electrocardiography Where possible they should be transferred, at an early stage, to a centre where hæmodialysis is available, if control by conservative therapy seems unlikely to prove adequate Dialysis should be considered at a relatively lower level of serum-potassium than is customary, in view of the great risk of further sudden releases of this cation into the circulation as muscle breakdown continues

In conclusion, it is emphasised that the cause of this accident was the victim's ignorance of the mechanism of gas-heating Visitors from overseas who are unfamiliar with the use of coal-gas should be instructed in its dangers

Summary

A case of fatal renal damage following skeletal muscle necrosis in carbon-monoxide intoxication is described The clinical course was that of acute, oliguric renal failure with terminal hyperkalæmia.

Postmortem examination revealed extensive muscle necrosis in one lower limb, and the changes of acute tubular necrosis with pigment casts in the kidneys

Our thanks are due to Dr G L B Thurston, H.M. Coroner, London, West District, Dr M D Milne, and Dr N F Coghill for advice and permission to publish, and to Prof T Crawford for the photomicrographs

References at foot of next column

Preliminary Communication

SELECTIVE PLACENTAL TRANSFER OF SERUM-PROTEINS IN THE RHESUS

THE transfer of antibodies from mother to young before and after birth has been studied in many laboratory animals and in man[1] Nearly all the evidence for their transmission to the fœtus has been based on immunological studies comparing the titre of specific antibodies in maternal blood with their titre in fœtal or cord blood. Although it has been assumed that in man their transfer is directly via the placenta, comparative studies in orders other than the primates have led Brambell et al[2] to suggest that the route in primates may be via the amniotic fluid, selection of γ-globulins taking place at the entodermal lining of the fœtal gut.

The transmission of other serum-proteins from mother to fœtus has received little attention Whipple et al[3] studied the transfer of ^{131}I-labelled serum-proteins in rabbits and dogs Labelled protein (unspecified) was found in the rabbit fœtuses but not in the dog The transfer of heterologous albumin has been demonstrated in the rabbit, using immunological measurement[4] So far, however, there has been no study of the transmission of homologous serum-proteins to the fœtus of any animal

Since a hæmochorial placental system comparable to that of man is found only among the catarrhine and anthropoid primates, the problem in relation to man can be investigated only in Old World monkeys or in apes The placenta of the rhesus (catarrhine) comes to resemble the human placenta very closely in the later stages of pregnancy[5]

We present here evidence of the selective transmission of whole homologous serum-proteins from mother to fœtus in the rhesus monkey, and demonstrate that the amniotic fluid plays an unimportant part in the transfer of whole serum-proteins

MATERIALS AND METHODS

Pregnant rhesus monkeys (*Macaca mulatta*) (B, C, D, and F) weighing 6–8 kg, and a green monkey (*Cercopithecus æthiops*) (E) weighing 5 2 kg, were used The monkeys were estimated to be within 4–6 weeks of the end of their gestation period (6 months) A sample of their blood was taken, and they were then given iodide water (0·02% NaI) to drink ad libitum for 1–2 days before the experiment and throughout its duration. Of this sample 0 3 ml of serum was iodinated with an average of not more than 1 atom of iodine per molecule of protein.[6]

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[1] Brambell, F W R. Hemmings, W A., Henderson, M Antibodies and Embryos. London, 1951
[2] Brambell F W R., Brierley, J, Halliday, R., Hemmings, W A *Lancet*, 1954, i, 964.
[3] Whipple, G H., Hill, R. B, Terry, R., Lucas, F V, Yuile, C L. *J exp Med* 1955, 101, 617
[4] Schechtman, A. M., Abraham, K. C. *Nature, Lond* 1958, 181, 120
[5] Amoroso E. C. in Marshall's Physiology of Reproduction, vol 2. London, 1952.
[6] McFarlane, A. S *Nature Lond* (in the press)

DR. LOUGHRIDGE AND OTHERS REFERENCES

Fahlgren, H., Hed, R., Lundmark, C. (1957) *Acta med. scand* 158, 405
Fowler P B S (1954) *Lancet*, i 240
Gordon B S, Newman, W (1953) *J Bone Jt Surg* 35A 764
Günther H. (1921) *Z klin. Med* 92, 41
Hed R. (1955) *Acta med scand.* suppl 303
Hedinger, C. (1948) *Schweiz med Wschr* 78, 145
Jasznik, B, Brasch, H. (1952) *ibid* 82 29
Larrey, D J (1812) Mémoires de chirurgie militaire, et campagnes vol 3 Paris
Mautner L S (1955) *A.M.A. Arch Path* 60, 136
Schürmann G (1921) *Dtsch Arch klin Med* 135 336
Touze J Thomas, M. (1952) *Bull Soc med Hôp Paris* 68 971

The doses prepared contained 1 6–1 8 mC of ^{131}I in 20 mg of serum-proteins(350–400 million counts per min), of which less than 2% was free iodide

Undialysed serum-protein samples (1 0 ml) were separated by electrophoresis in borate buffer (μ=0 05, pH 8 5) on treated cellulose columns The columns (38 × 1 cm) were developed for 8$^1/_2$ hours with 600 volts The proteins were eluted with buffer in 2 ml fractions γ-globulins in unhæmolysed serum samples were isolated after dialysis against 0 02 M phosphate buffer (pH 6 2) on 1 g columns of diethylaminoethyl cellulose (D E A E)[7] and eluted with buffer in 2 ml fractions Most serum and liquor samples were also similarly fractionated after passing through ‘Deacidite’ FF (Permutit Co , an anion exchange substituted polystyrine, 100–200 mesh, in sodium form) used to adsorb residual free iodide after iodination of the dose Radioactivity was measured in a well-type scintillation counter with an efficiency of 16 2% for ^{131}I and a background of 130 c per min All samples were counted for a minimum of 4000 counts, except for very weak samples on column fractions which were counted for 1000 counts The protein in each column fraction was measured at 280 mμ in a ‘Unicam’ spectrophotometer and then counted

Red blood-cells taken from the mother at the same time were labelled with 0 8–1 0 mC carrier-free ^{51}Cr for an hour at room temperature in acid citrate dextrose (A C D) After washing thoroughly in saline (final activity=37,000 c per min per mg Hb) they were stored in A C D at +4°C until use within 24 hours Fœtal red cells were washed in saline (6 × 15 ml) and 3 ml of packed cells counted in the scintillation counter

EXPERIMENTS ON TRANSPLACENTAL TRANSFER

(Monkeys B, C, and D)

Procedure

The ^{131}I-labelled serum was mixed with the ^{51}Cr-labelled red cells and injected intravenously into the mother Anæsthesia was induced 8–9 hours later with thiopentone and maintained with cyclopropane in closed circuit or with open ether The lower segment of the uterus was incised down to the level of the fœtal membranes, and through an avascular part 20–80 ml of blood-free amniotic fluid was aspirated with needle and syringe The fœtus was delivered and exsanguinated immediately by open heart puncture A sample of maternal blood was taken just before or just after delivery of the fœtus

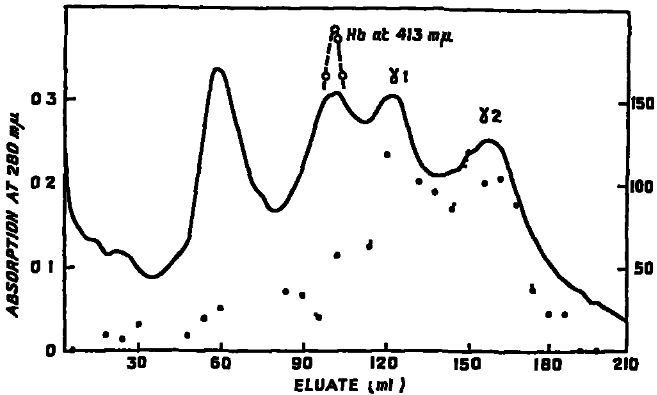

Fig 3—Eluate of column electrophoresis of 1 0 ml of fœtal serum (untreated) showing the presence of labelled γ1 and γ2 globulin 8 hours after the dose (monkey C)

Results

3 ml of packed fœtal red cells gave a count not significantly above background, indicating that there had been no gross contamination with maternal blood due to accidental hæmorrhage in utero Column electrophoresis of the ^{131}I-labelled dose in carrier serum indicated that, although the specific activity of the albumin peak was always 2–3 times the specific activity of the globulins, the count pattern followed the protein (absorption at 280 mμ) pattern closely About 80% of the total counts were with the albumin, about 4% in the γ-globulin isolated chromatographically, and, by difference, about 16% in the other globulins Fœtal serum (fig 1) contained radioactivity in the albumin peak and γ-globulin-fraction peak Some of the activity of the albumin appeared to be due to adsorbed free ^{131}I iodide, which was removed by deacidite FF (fig 2) Dialysis for 48 hours in 5% NaI failed to reduce the specific activity any further There were almost as many counts in the γ-globulin as there were in the albumin, indicating that

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7 Peterson, E A , Sober, H A *J Amer chem Soc* 1956 ,78, 756

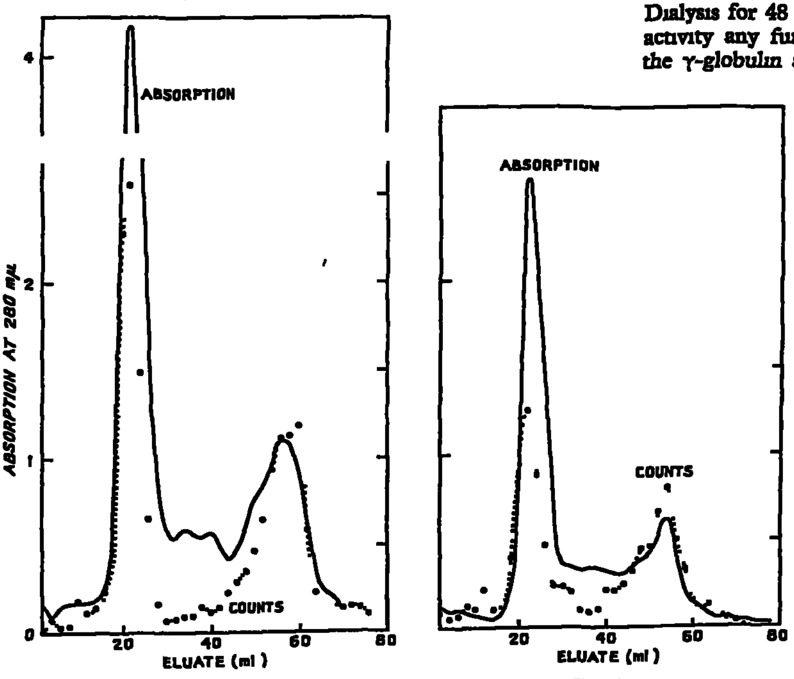

Fig 1 *Fig 2*

Figs 1 and 2—Eluate of column electrophoresis of 1 0 ml of fœtal serum untreated (fig 1) and after treatment with deacidite FF and dialysis against 5% NaI and 0 01% monoiodotyrosine (fig 2) (Monkey D, 8 hours after the dose) This shows the presence of radioactive albumin and γ-globulin (dotted line

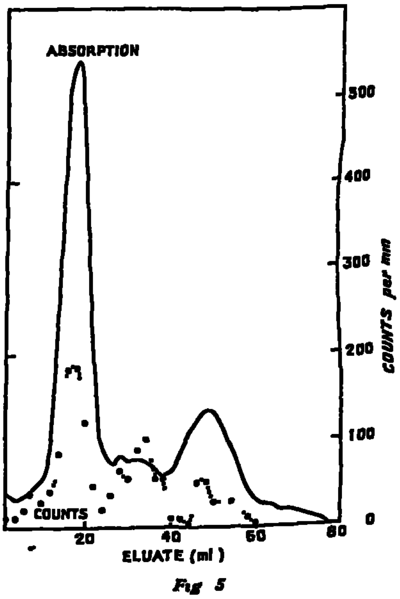

Fig 5

Fig 5—Eluate of column electrophoresis of 1 0 ml fœtal serum after treatment with deacidite FF (monkey F), 24 hours after injecting into the amniotic fluid the same amount of radioactive serum-proteins as was used for transplacental experiments B, C, and D There is little absorption of any specific labelled protein

γ-globulin was transmitted to the fœtus some 15–20 times more easily than albumin. Moreover, the γ-globulin isolated by D.E.A.E chromatography accounted for almost all the counts in the β and γ globulin fractions Fig 3 shows that prolonged column electrophoresis demonstrated the presence of both 1 and γ2 labelled globulin

Electrophoresis (fig 4) showed that the specific activity of the albumin in the amniotic fluid was about 5 times that of the albumin in the fœtus, but apparently no other labelled protein was present in significant quantity The amniotic fluid of the rhesus and green monkeys contained large amounts of a protein which moves on column and paper electrophoresis in the region of the α1 and α2 globulins, no peak of radioactivity was present in this position.

EXPERIMENTS ON ABSORPTION OF SERUM-PROTEINS FROM AMNIOTIC FLUID

(Monkeys E and F)

Procedure

Maternal serum-proteins prepared in the same way were injected percutaneously into the amniotic cavity, using a no 23 gauge needle in the conscious animal, after mixing with 3 ml of amniotic fluid removed previously through the same needle Samples of the fluid were taken at operation 8 hours later (E), and at 3 hours and 6 hours by aspiration through the abdominal wall and at operation 24 hours later (F) Cæsarean section was performed samples of amniotic fluid uncontaminated with blood, and of maternal and fœtal blood, were taken, and the samples were fractionated

Results

The same total amount of activity was injected into the amniotic fluid (volume 100–120 ml) as was injected intravenously in monkeys B, C, and D whose intravascular plasma volume was estimated to be about 250–300 ml

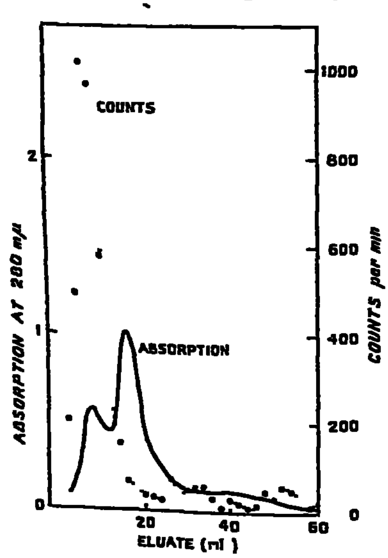

Fig 4—Eluate of column electrophoresis of the concentrate of 4·0 ml of liquor after treatment with deacidite FF (monkey D), 8 hours after the dose The protein pattern shows a small amount of albumin and a large amount of another protein in the α1 and α2 globulin position. Labelled albumin is present but no other significant peak of radioactivity in the region of the globulins

The specific activity of the albumin in the liquor of E and F obtained at 8 and 6 hours after injection was about 100 times greater than that present in the liquor at operation in monkeys B, C, and D Fig 5 shows that, after absorption of the iodide bound to albumin by passing through deacidite FF, only very small quantities of labelled proteins were present in the fœtal serum even after 24 hours Electrophoresis of serum mixed with the contents of the duodenum and jejunum, and the ileum of the fœtus of E, showed an almost normal pattern of labelled serum-proteins present in fairly high concentration. The fœtus had therefore swallowed liquor and had the opportunity to absorb proteins from the gut, and at least some of all the major components of serum-proteins had escaped digestion. The maternal serum at operation 24 hours after the dose (F) contained small quantities of labelled albumin, assuming that it had equilibrated throughout the whole albumin pool of the mother, this labelled albumin would account for very roughly 0 1% of the dose albumin Some of this might well represent some of the dose that had leaked out through the three needle tracks made through the fœtal membranes

DISCUSSION

The validity of these experiments rests on the biological normality of the ^{131}I-labelled proteins

There is now reasonable evidence that proteins iodinated with an average of 1 atom per molecule behave metabolically with close similarity to proteins labelled with ^{14}C-aminoacids, at any rate in rabbits [8 9] If labelled proteins are allowed through the placenta, then one may fairly assume that unlabelled ones can also pass Exact measurements of labelled proteins (albumin in particular) were difficult because of the tendency to adsorb free labelled iodide, which from trichloracetic acid (T C A) precipitation studies was found to be present in relatively high concentration in fœtal serum and liquor, even in the presence of carrier It is believed, however, that passing the serum through deacidite FF stripped most, if not all, of this adsorbed iodide

The experiments demonstrate two main points First, they show the direct transmission of homologous maternal albumin and γ-globulin to the fœtal circulation, this transfer is selective in that γ-globulin is transmitted some 15–20 times more easily than albumin Globulins with a mobility in the α2 and β globulin region (in the conditions of electrophoresis used) do not appear to reach the fœtal circulation This is in accord with the prediction based on studies on changes in protein-fraction concentrations in infants and children [10] Selectivity of serum-protein transfer has been demonstrated (for homologous and heterologous serum-proteins [11] and for homologous and heterologous antibodies [12] by the endoderm of suckling rats Selection of proteins in the rabbit is known to be controlled by the yolk-sac splanchnopleur, which is also entodermal [1 13 14] The transplacental selectivity in the monkey thus appears to be one of the rare instances of selection by a non-entodermal surface The selection of particular types of homologous antibody [15–20] illustrates how discriminating the human placenta can be

Secondly, it has been shown that the transfer of the albumin and γ-globulin to the fœtus is not via the amniotic fluid but is presumably transplacental In the late stages of pregnancy very little, if any, of the proteins was absorbed unchanged from the amniotic fluid This was predicted for antibodies by Wasz-Hockert et al [21] who found that in newborn infants with partial and complete œsophageal atresia the blood-level of diphtheria antitoxin was comparable with that of normal infants The likelihood that proteins are absorbed from inhaled amniotic fluid also becomes remote

The protein composition of the amniotic fluid of the rhesus monkey near term was, however, different from that of human amniotic fluid at term The total protein concentration was about one-tenth that of serum, there was a small amount of albumin, and very small quantities of β and γ globulins About 60% of the protein was of low

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[8] McFarlane, A S *Biochem J* 1955, 62, 135

[9] Cohen, S , Holloway, R C , Matthews, C M , McFarlane, A S *ibid* p 143

[10] Josephson, B , Gyllensward, C *Scand J clin Lab Invest* 1957, 9, 29

[11] Bangham, D R , Terry, R. J *Biochem J* 1957, 66, 579

[12] Halliday, R. *Proc. roy Soc.* B 1955, 143, 408

[13] Hemmings, W A , Oakley, C. L *ibid* 1957, 146, 573

[14] Hemmings, W A *ibid* 1957, 148, 76

[15] Munk-Anderson, G *Acta path microbiol scand* 1956, 39, 407

[16] Rozansky, R., Bercona, B *Proc Soc exp Biol , N Y* 1956, 92, 4

[17] Neter, E *ibid* 1957, 96, 488

[18] Timmerman, W A *Z ImmunForsch* 1931, 70, 388

[19] Adamson, C. A., Lofgren, S , Malmomis, C *Scand J clin Lab Invest* 1951, 3, 52

[20] Jacobowicz, R., Bryce L. M *Med J Aust* 1951, 1, 365

[21] Wasz-Höckert, O , Wager, O , Hautala T Widholm O *Ann Med exp Fenn* 1956 34 444

molecular weight, and on electrophoresis, under the conditions used, it travelled between the $\alpha1$ and $\alpha2$ globulin Whereas labelled albumin passes to the amniotic fluid from the maternal circulation, only very small quantities, if any, return to the mother Since so little gets into the fœtus we infer that there is proteolysis within the amniotic cavity

These points are under investigation, and a further report, with a quantitative analysis of the above experiments, will be given in due course

SUMMARY

The transfer of ^{131}I-labelled serum-proteins from the maternal circulation to the fœtal circulation has been investigated in near-term pregnant rhesus monkeys

The direct transfer of labelled $\gamma1$ and $\gamma2$ globulin has been demonstrated Albumin is transmitted with much less relative facility, and little, if any, other globulin is transferred Only labelled albumin was found in the amniotic fluid

Labelled maternal serum-proteins injected into the liquor were not found in the fœtal circulation 24 hours later Only extremely small quantities were found in the maternal circulation

The transfer of γ globulin is thus shown to be transplacental in one species of primate, and the placenta is shown to be another rare example of a non-entodermal membrane capable of selective transmission of protein'

It is a pleasure to thank Dr A S McFarlane and Mr R C Holloway for assistance in preparing the labelled serum, Dr K Sykes and Dr P Frost for help with anæsthesia, and Dr C P Farthing and Mr W B Brocklehurst for help at operations, and Mr D Short and Dr F Hawking for assistance in obtaining the monkeys

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Reviews of Books

The Kidney

An Outline of Normal and Abnormal Structure and Function

H E DE WARDENER, M B E , M D , F R C P , senior lecturer in medicine, St Thomas's Hospital, London London J & A Churchill 1958 Pp 338 45*s*

THERE are a number of books on the kidney in which physiologists lay down canons of behaviour for the diseased kidney, or pathologists infer from their sections how the kidney must have behaved in life Neither approach has been particularly helpful in the practical management of renal disease, whose study has on the whole progressed through the recognition of clinical syndromes which can be investigated and treated even when their precise ætiology may be a matter of surmise Fuller Albright is reported to have said that we may soon know everything that matters about rheumatoid arthritis, except its cause and cure, a similar thrust could be made at our present clinical approach to renal disease, but a reading of Dr de Wardener's book goes far towards rebutting it

The background of physiology and the description of syndromes are clearly presented, with the authentic touch of the contributor to knowledge and there is also a good, if brief, account of the contribution which renal biopsy and other techniques can make to ætiological diagnosis, a proper emphasis on the importance of the treatable disease, acute pyelonephritis, some indication of the complicated relationship between renal disease or dysfunction and hypertension, œdema, and extrarenal disease, and an adequate survey of available treatment

The manner of presentation sometimes fails to equal the excellence of the matter The sequence of short and unrelated chapters towards the end of the book is irritating, and some rearrangement might help the reader here, though a sentence like the penultimate one on p 247 would defy interpretation in any context, unless perhaps A C T H is a misprint for A D H or D C A Most of the illustrations and charts are helpful, but those students with a perverse appetite for complexity will find satisfaction in figs 36 or 37

These criticisms must not obscure our view that this is a stimulating and valuable textbook, which should be read by all students of renal disease We hope that Dr de Wardener, having achieved a masterly synthesis of refractory material, may go on to excel himself in clarity in the second edition

Leptospirosis in Man and Animals

J M ALSTON, M D , F R C P E , Whittington Hospital, London , J C BROOM, O B E , M D , Wellcome Laboratories of Tropical Medicine, London Edinburgh and London E & S Livingstone 1958 Pp 367 40*s*

THERE is a lot to be said for the monograph The textbook of medicine tells us only so much bacteriology as is useful in diagnosis, that of bacteriology lays more emphasis on morphology and systematics than on epidemiology This monograph includes both and adds much more, and by its wider view allows us to make some reasonable guesses at the place in Nature of the genus Leptospira For many years the authors have been recognised as the final court of appeal in their subject Not only have they added much to knowledge but they have been liberal in their help and advice to others They seem to have read everything which has been written in all civilised tongues and they are generous in their acknowledgment of the pioneer work of the others whose portraits add interest to their book

It would be both pointless and ungrateful to search for omissions a frustrated reader can be assured that a letter to the authors will obtain a speedy and helpful reply The only suggestion which we would dare to make is that the future editions might benefit by the collaboration of a veterinary surgeon By that time it may be easier to be dogmatic on the importance of the infecting strain of leptospira We believe that in man *Leptospira icterohæmorrhagiæ* and *L canicola* produce related but not identical ailments Is there any virtue for the physician in distinguishing between infection with, say, *L australis A* and *L australis B* ? Similar problems are obvious in other branches of bacteriology (for example, with staphylococci and salmonellæ) and the answers may have considerable effect upon the future of diagnostic bacteriology

Psychiatry in the Modern World

E B STRAUSS, M A , D SC , D M , F R C P , lately physician in psychological medicine, St Bartholomew's Hospital, London London Michael Joseph 1958 Pp 70 8*s* 6*d*

IT has always been a pleasure to sit at the feet of Dr Strauss, and his many disciples will not be disappointed with this little book Drawing from his five recent articles in the *Sunday Times*, he discourses amiably about psychiatrists and psychologists, manic-depressives and schizophrenics, psychosomatics and somatotypes always clear, always sensible, and often stimulating The title may suggest a larger or more ambitious work, but the author himself admits he only touches on " the fringe of the fringe " It is a model of psychiatry made easy, however, and can be recommended to the lay public, to students, or to doctors who are looking for " an introduction to an introduction "

Especially commendable about the book is the author's neglect of sensation and his relative self-effacement it is all too easy for the writers of such books to glorify the Ego with long accounts of interesting cases completely cured and invidious comparisons of the views of others with their own Perhaps we should call a halt to these little books now, until there are some new advances for the public to be told about it will in any case be hard to improve on the writing in this one But why does Dr Strauss think that " shock therapy " is an inappropriate name for E C T ?

THE LANCET
LONDON 16 AUGUST 1958

Effects of Radiation

SINCE the Medical Research Council's committee on radiation hazards made its report [1] in June, 1956, many new data on the biological effects of ionising radiations have been assembled, but the United Nations report,[2] made known on Sunday, shows that more than two years of intense study and analysis have not elicited answers to some disturbing questions The doubt remaining at the root of all disquiet is whether or not there is a threshold at which radiation damage begins and below which no harm results The United Nations committee (whose report is described on p 360) cannot answer this question (indeed, it is doubtful whether it will be answered in the near future) So the fears we expressed [3] two years ago, and to which we have returned from time to time, remain unrelieved

The genetic damage which additional radiation may induce and which may be manifest in later generations has been in the forefront of discussion The medical applications of radiation are here the greatest hazard—in countries where such applications are common The M R C report estimated that diagnostic radiology in Britain contributed a population gonad dose of at least 22% of natural background radiation, and the United Nations committee confirm the "at least" when they say that the values put before them for the genetically significant doses from medical procedures are "of the same order" as the doses from natural sources Background radiation supplies an estimated genetically significant dose of 3 rem in thirty years, and man-made sources (excluding environmental contamination and occupational exposure) are put in the range 0 5–5 rem For this total, diagnostic X-ray examinations are largely responsible, and 80–90% of the diagnostic dose to the gonads comes from a few types of abdominal and pelvic examination The reinforced lesson in these new estimates is that greater efforts must be made to restrict the gonad dose in medical irradiation, and stricter judgment must be used before patients are exposed to the crucial pelvic and abdominal investigations Detailed inquiries into doses administered in radiological practice are in hand in this country and elsewhere, but there is no need to wait for more facts before renewing the advice of the M R C committee that "the time has come for a review of present practice in diagnostic radiology" What has been made known in the past two or three years has already prompted caution in the medical use of radiation alarms should not be so vivid that valuable information is left unsought when it may be of vital concern to the patient, but the words of the U N report must now add a new warning "Medical and industrial procedures tending to increase radiation levels to which human populations are exposed should be carefully weighed as to such benefits or hazards as they may have"

Radiation-induced mutations are in general harmful, and increase in direct proportion to the genetically significant exposure, even at very low doses, and this accepted qualification must temper the apparent reassurance provided by the committee's figures for the genetic effect of environmental contamination by radioactive substances released in the testing of nuclear weapons If weapon tests cease this year the thirty-year "genetic" dose is put at 0 010 rem (which agrees with the M R C committee's view of "less than 1% of natural background") If tests continue according to either of the two assumptions set out on p 361, this dose may increase to 0 06 or 0 12 rem (2% or 4% of background) From these and many other figures before them the U N committee assess ("with wide margins of uncertainty", particularly about the dose required to double the mutation-rate) that a situation of fallout equilibrium, reached after long-continued testing, may be associated with from 500 to 40,000 annual instances of major genetic defect, compared with an estimated natural occurrence of 700,000 to 3 million yearly among a future world population of 5000 million The existing and expected "normal" burden of genetic defect is enormous the estimated addition by fallout is slight, but it is nevertheless an addition

When they come to put a value on the somatic risk, on what may happen to those now living as a consequence of man-made contamination of the environment, the U N committee are more perturbing People who derive most of their dietary calcium from rice and vegetables may experience a mean marrow dose of 7 5 or 17 rem over seventy years if weapon tests continue to equilibrium under one or other of the committee's assumptions In the same period natural sources give an estimated marrow dose of 7 rem Even if weapon tests stop this year, a seventy-year marrow dose of 0 96 rem is possible from fallout products This is a dose equivalent to slightly more than that delivered by 10 strontium units, and the M R C report said that "immediate consideration would be required" if the concentration of radioactive strontium in human bones showed signs of rising greatly beyond 10 strontium units For milk-drinking, rather than rice-eating, peoples the outlook is better At the highest estimate the marrow dose from fallout products will be 2 8 rem in seventy years, and if tests stop now the dose may be limited to 0 16 rem These figures, however, can be given very different meanings while nothing certain is known about thresholds Thus, on the assumption that there is no threshold for leukæmia the U N report estimates that equilibrium fallout may eventually mean 5000 to 60,000 cases of leukæmia a year But if a threshold is put at 400 rem it is unlikely that there will be any additional leukæmia If there is no threshold and tests stop soon, 400–2000 leukæmias a year may temporarily result, if 400 rem is the key level, nothing Even though these estimates are admittedly very uncertain, they must be respected for the long and careful judgment that backs them They are a warning of what *may* happen if the release of radioactive poisons is allowed to continue

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[1] Hazards to Man of Nuclear and Allied Radiations Cmd 9780 H M Stationery Office

[2] Report of the United Nations Scientific Committee on the Effects of Atomic Radiation New York, 1958 Obtainable from H.M Stationery Office P O Box 569, London, S E 1 Pp 228 18s

[3] *Lancet*, 1956, i, 999

As an agreed international statement of opinion based on as wide a survey as possible, the U N document is a notable achievement Its confirmation of so many of the findings of the M R C committee, pronounced more than two years ago, is a striking tribute to that committee

Fertility and Mental Illness

The extent to which people liable to mental affliction procreate has long concerned those administering mental-health policy Between the wars large families among the lower social classes led to fears (now largely dissipated) about declining national intelligence and to the closely related fear that unrestricted breeding among stock of poor mental background was creating an increasing problem of mental disorder Beliefs have sprung up with the most far-reaching effects sterilisation schemes—voluntary, pseudo-voluntary, and compulsory—have been advocated Prof Glanville Williams[1] has given us the most up-to-date and comprehensive survey of the approaches to sterilisation here and in America and argues persuasively for legalisation and wider use, although some of his grounds must remain open to question The importance of these issues and the power with which views on them are expressed make it appropriate that Prof Aubrey Lewis should have examined in detail some of the evidence His critical survey of work on the fertility of the mentally ill (but not of the mentally defective) in a Galton lecture[2] shows how few and contradictory are the facts so far obtained

He pointed out that a hundred years ago the concept of " degeneracy " was put forward by Morel,[3] and until the turn of the century it was thought that inferior stock underwent decay generation by generation, psychopathy breeding neuroses, then at a younger age schizophrenia (the origin of the term " dementia præcox "), the line being extinguished when idiocy in childhood precluded further procreation Such a tidy scheme fitted in well with current religious beliefs on reprobation and the sins of the forefathers being visited on the children, and with Lombroso's views on atavism and criminal types Henry Maudsley[4] in 1862 subscribed to it, and even Adolf Meyer agreed But in the early 1900s the pendulum swung to the other extreme, and David Heron[5] in 1907 expressed the belief that marriages of the insane were *more* fertile than others The idea of Nature's beneficent hand extinguishing its less useful members was now replaced by a fear of unrestricted proliferation among the mentally diseased Despite the exposure of fallacies in method and reasoning, the belief persisted, and it was not until the 1930s that the matter was really put to the test Dahlberg[6] in Sweden and Dayton[7] in the U S A showed independently that the pre-admission fertility of insane married women was significantly *lower* than among a comparable group of women in the general population It remained for Professor Essen-Möller[8] in Sweden to compare the two main diagnostic categories—manic-depressives and schizophrenics From a group of nearly 5000 married patients he deduced that manic-depressives were about as fertile as the general population The schizophrenics, on the other hand, were as a whole about a quarter as fertile as the general population, but more detailed analysis showed that schizophrenic men before their illness had average fertility, whereas women were about half as fertile as normals Over the years both sexes followed the national decline in birth-rate more slowly than was expected, until the pre-schizophrenic women were about as fertile as normals After the onset of the illness the birth-rates, as expected, fell greatly Patients who married after the illness (presumably mild) had developed were normally fertile Paradoxically the birth-rate was higher than expected in the year before admission On close examination this seemed to be a sociopsychological phenomenon due to postponement of admission until after the birth More recently Böök,[9] surveying a shut-off community in North Sweden, found that the fertility of marriages contracted by schizophrenics was very slightly *greater* than normal, but fertility of the unmarried schizophrenics was lower than among others, and as 75% of the men were single the over-all fertility was well below that of the normal population It appeared, therefore, that lowered fertility among schizophrenics might be an index of the lower chances of marriage rather than an effect of the disease itself The preponderance of single persons over married among schizophrenics has often been noted, Norris,[10] for example, found in English male patients about six times as many unmarried as married on first admissions The most probable reason seemed to be that the premorbid " schizoid " personality makes marriage less likely, although the protective effect of an affectionate home life and enhanced likelihood of being sent to hospital may play a part A man who is shy and indrawn is at a special disadvantage in our culture, whereas a woman of this type is more likely, perhaps, to contract matrimony It is evident, though, from Böök's figures that the probabilities vary in different environments his schizophrenic women had a much better chance of marriage than those of other communities studied

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[1] The Sanctity of Life and the Criminal Law London, 1958

[2] *Eugen Rev* 1958, 50, 91

[3] Morel, B A Traité des dégénérescences physiques, intellectuelles, et morales de l espèce humaine Paris, 1857

[4] *J ment Sci* 1862, 8, 61

[5] A First Study of the Statistics of Insanity and the Inheritance of the Insane Diathesis London, 1907

[6] Dahlberg, G *Z ges Neurol Psychiat* 1933, 144, 427

[7] Dayton, N A *Stud quant cult Sociol* 1930, 24, 123 New Facts on Mental Disorders Springfield, Ill , 1940

[8] Essen-Möller, E *Acta psychiat , Kbh* 1935, suppl 8 *Arch Rass- u GesBiol* 1936, 30, 367

[9] Böök, J A *Acta genet* 1953, 4, 133

[10] Norris, V A *J ment sci* 1956, 102, 467

Having concluded that the fertility of schizophrenics was low, Professor LEWIS considered the possible factors maintaining the disease at its present level he subscribed to the view that spontaneous gene mutation occurs at a high rate, and he called attention to the Medical Research Council report on the possible effects of radiation [11] Mental illness, it said, is the most important single category of disease determined largely by heredity, and he believed that increased radiation may be raising the mutation-rates for these diseases

The fertility of neurotic persons is almost completely unknown One study [12] suggested a vague link between small families and feelings of inadequacy in the parents, but unpublished work at the Maudsley Hospital on a limited sample has shown no differences in fertility or in the number of single women The psychological mechanisms believed to play a part in sterility, and the sexual disturbances which so often plague the neurotic, may be expected to affect birth-rate, but so far nothing has been proved

Professor LEWIS speculated on the possible consequences of present mental-hygiene campaigns, which, very laudably, seek to instil into the public a more sympathetic and informed understanding of mental illness To play down the differences between mental and physical illness, and to ignore the genetic implications, might, he suggested, lead to higher marriage-rates among those liable to manic-depressive illness or with a schizoid personality a contributory factor might be the increasing use of treatment in the community and shorter periods in hospital With increased birth-rates among these groups there would be more children destined to become mentally ill, and such children would be in the care of parents liable to spend periods in mental hospitals—a thing which he felt no humanitarian person could regard with equanimity On this most important subject we agree with Professor LEWIS that hereditary factors should be squarely faced both by ourselves and by the public, and that the risks of marriage and procreation should be made known as fairly as possible in the light of present knowledge this is already the standard practice in the case of epilepsy, where commonly the normal marriage partner undergoes electroencephalographic examination in order that the chances of epilepsy in the children may be assessed While no-one would wish to ignore the effects of environment in the formative years of life, the psychodynamic view of causation must not be allowed to obscure the work of KALLMANN [13] and others on heredity No person must be deprived, against his will, of the fundamental right to procreate (especially at our primitive level of knowledge), but we as doctors would be doing less than our duty if we did not place the facts, as far as they are known, before our patients and the public Further work is badly needed, and no-one is better placed than Professor LEWIS to see that it is properly carried out

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[11] Hazards to Man of Nuclear and Allied Radiations H.M Stationery Office, 1956

[12] Westoff, C F, Kiser, C V *Millbank Mem Fund Quart* 1952, 30 239

[13] Kallmann, F J Heredity in Health and Disease New York, 1953

The Anatomy of the Cardia

FOR some time investigation of the lower œsophagus was out of phase, for diseases in this region were well documented while anatomical study lagged behind In hypotheses about the mechanism of closure at the cardia, extrinsic pinchcocks replaced intrinsic valves, while deviationists concerned themselves with the acuteness of the angle between œsophagus and stomach Recently, however, intrinsic valvular mechanisms have returned to favour By marking the anterior edge of the diaphragmatic hiatus at operation with a clip, BOTHA showed that the manner in which the crura embrace the œsophagus at the hiatus can have little effect on the closure mechanism, for when the diaphragm contracts the gastric fundus is pushed downwards in relation to the hiatus,[1] thus opening the gastro-œsophageal angle and vitiating any sling effect the crura might have at that point. Radiographically controlled studies undertaken by him with ASTLEY and CARRÉ [2] pointed to the lower œsophagus as an area which, in the majority of the 18 persons investigated, provided a pressure "barrier" between stomach and upper œsophagus, this lay above the level of the hiatus ATKINSON et al [3] confirmed this finding, they showed that the pressure differentials were removed by swallowing, and that in cases of reflux the pressure barrier was absent That the barrier in no way relies on the diaphragm for its existence they proved conclusively by demonstrating its presence in a case of hiatus hernia without reflux when the barrier was quite definitely above hiatal level In a converse fashion they found that the barrier was eliminated in a case subjected to Heller's operation when particular care had been taken not to damage the hiatus From their radiographic studies they were likewise unable to demonstrate any correlation between reflux and angle of entry of the œsophagus into the gastric hernia in cases of hiatus defect The recent findings thus suggest that a sphincter exists, if not in the palpable anatomical sense, certainly in the all-important functional sense, and in this respect JOHNSTONE's [4] report of a woman who suffered œsophageal reflux only when tired is of interest The understanding of reflux has now a firmer basis, and treatment of œsophagitis, particularly as regards surgical technique, can be designed more rationally

BOTHA [5] has now added to knowledge of the gastro-œsophageal junction by showing that many people have mucosal folds which, when drawn together, act as a cork to close the top of the stomach These folds are not valvular and mechanical but are thrown up longitudinally by contraction of muscularis mucosæ The presence of such folds has been in doubt since MAGENDIE first described them, indeed BOTHA's work left him in doubt until he began to study the living organism instead of specimens (The pathological condition of lower œsophageal ring appears to be due to hypertrophy of the muscularis mucosæ at this site [6], but the outcome is a horizontal shelf) It should occasion no surprise that several factors combine to ensure closure of the cardia, for most physiological mechanisms are complex, BOTHA hints that the relative importance of each factor varies from one person to another

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[1] Botha, G S M *Lancet*, 1957, i, 662

[2] Botha, G S M, Astley, R., Carré, I J *ibid* p 659

[3] Atkinson, M, Edwards, D A W, Honour A J, Rowlands, E N *ibid* 1957, ii, 1138

[4] Johnstone A S *Brit J Radiol* 1955, 28, 2

[5] Botha, G S M *Brit J Surg* 1958, 45, 569

There is need for further anatomical study to establish whether or not columnar epithelium in the lower œsophagus is a variant of normal, BARRETT [7] regards its presence there as abnormal and speaks of those with this condition as patients, even though they may be symptom-free, ALLISON and JOHNSTONE [8] presumed that the presence of gastric mucosa of cardiac type in the œsophagus may be a congenital abnormality Yet BOTHA finds that the junction of squamous and glandular epithelium is above the cardia in most people Does it really matter? The discussion which this "ectopic" epithelium has provoked seems to be out of proportion to its probable importance A full study of this histological point should give a firm statistical answer which might remove one distraction in arguments on the causation of peptic ulcer of the œsophagus And if anyone has difficulty in differentiating œsophagus from stomach (as BARRETT [7] points out, the presence of mucosa is the usual indicator) then the pressure barrier might aid in defining the lower limits of œsophagus

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Annotations

B C G IN THE U S A

A LARGE trial of B C G vaccination in the U S A has been described by Palmer et al [9] This took place in two localities—Puerto Rico and two counties in Georgia and Alabama The groups studied differed considerably and were apparently subject to different risks of tuberculosis, they are therefore considered separately The Puerto Rican population consisted of children and adolescents under 19 years of age, whereas the population studied in Muscogee and Russell counties contained people of all ages, more than half being over 19 and almost a fifth 40 years old or more Among the 191,827 young Puerto Ricans there were about 40% "positive" to a 10 T U Mantoux test, among the 16,125 under 20 in Muscogee and Russell only 14% were "positive" to a 5 T U test The tuberculin-negative individuals in both trials were divided into vaccinated and unvaccinated groups The morbidity experience of the three groups—initially infected, vaccinated, and unvaccinated—was compared over periods of six to seven years The measure of morbidity was obtained from the number of cases of tuberculosis known to have arisen within these groups through the existing medical, public-health, and vital statistics reporting systems in the two localities, the people in the trials were not individually followed up and examined

Although this method may enable valid comparisons to be made within the two populations studied, it does not permit accurate comparison between them or with other similar trials In Puerto Rico the average annual incidence per 100,000 was 163 among the initially infected, 43 among the initially uninfected and unvaccinated, and 30 among the vaccinated 856 (75%) of the 1149 reported cases of tuberculosis occurred in those found to be infected at the time they entered the trial In Muscogee and Russell the corresponding rates were 78, 22, and 14, and 161 (75%) of the 216 reported cases were in those already infected It was concluded that the reduction of tuberculosis attributed to vaccination was 31% in Puerto Rico and 36% in the Georgian and Alabama districts among those not already infected when the trial began If all the uninfected in the Puerto Rican group had been vaccinated there would have been a 7 9% reduction in known tuberculous morbidity in the whole population studied in the period of six to seven years, and a 9 3% reduction in Muscogee and Russell counties

The findings are compared with those of the rather more precise trial carried out by the Medical Research Council [10] In this, the estimated reduction in morbidity that could have been obtained (assessed by individual follow-up) over a period of two and a half years in the initially uninfected was reported to be 82%, compared with the reduction of only about 30% in the American trial These and other differences between the trials are discussed in the report, and it is concluded that the apparent differences in the effectiveness of B C G vaccination are inexplicable But the two trials are not comparable in many respects—in particular, the ages of the subjects The British trial concerned only children aged 14–15, adolescents approaching the time of leaving school The efficacy of vaccination among these may not be the same as among infants, young children, or adults, even of the same race and in the same environment

Palmer et al conclude that extensive vaccination is not indicated in the United States They state that "because B C G cannot help those who are already infected, nor those who will not become infected, and may be helpful only to a portion of the decreasing few who will become infected in the future, it is apparent that vaccination cannot be very useful in controlling tuberculosis in this country" Presumably this is meant to apply to all large-scale vaccination of groups of people, whether defined by age, or by special risk of exposure to infection (such as nurses medical students, laboratory workers, and the families of known tuberculous patients) The assertion loses some of its force by containing such an indefinite attribute as "very useful" To gain even a 30% chance of preventing tuberculous illness in a baby exposed to an infectious mother might be thought very useful by the parents, and to prevent one person within each affected household from becoming ill could be considered a very useful contribution to controlling tuberculosis within the community

Whether widespread and expensive public-health endeavours to vaccinate large numbers of people is justified can be determined only by taking into account epidemiological, economic, and political factors unknown to those who are not intimately acquainted with that community A recommendation to limit or avoid using B C G vaccination as a centrally controlled public-health measure may well be right in a particular situation But such a recommendation does not condemn vaccination in all other situations—as is clearly recognised by Palmer et al —or in individual cases A measure may not be very useful for maintaining the health of the public, but it may be invaluable for preventing an individual dying The committee on therapy of the American Trudeau Society has just issued a statement on the role of B C G[11] It states that B C G has a place in preventing tuberculosis and suggests certain groups in which it might profitably be used. These are almost the same as the groups now being vaccinated in Great Britain, with the exception of the adolescent children throughout the country, the committee including only children living in areas with a high prevalence of tuberculosis The statement concludes "It is the responsibility of the physician to weigh the advantages and disadvantages in a particular situation."

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[6] MacMahon, H E, Schatzki, R, Gary, J E *New Engl J Med* 1958, 259, 1

[7] Barrett, N R *Surgery*, 1957, 41, 881

[8] Allison, P R, Johnstone, A S *Thorax*, 1953, 8, 87

[9] Palmer, C E, Shaw, L W, Comstock, G W *Amer Rev Tuberc* 1958, 77, 877

[10] Medical Research Council *Brit med J* 1956, i, 413

SPREAD OF STREPTOCOCCI

THREE months ago[12] we drew attention to a current study by Holmes and Williams[13] of streptococcal infections and their probable sources among a large population of children in a residential Dr Barnado's Home over a period of 3½ years The reduction of so large a mass of epidemiological data to a useful form is no easy matter, Holmes and Williams have ordered their material so as to provide maximum information with maximum clarity in a way which deserves much admiration In their concluding chapters[14] they have attempted not only to assess the factors influencing individual susceptibility to streptococcal infection under institutional conditions but also to analyse the many differing effects which the organism, the host-carrier, the environment, and the method of treatment may have on the epidemic pattern in such a community

In the matter of susceptibility, the pros and cons of tonsillectomy have been much discussed Holmes and Williams' analysis shows that their tonsillectomised children individually derived moderate benefit, in that subsequently they suffered from few streptococcal sore throats The effect of tonsillectomy, however, seemed to be less in protecting the children's throats against colonisation by streptococci than in preventing clinical illness accompanying infection A potential social disadvantage which may follow tonsillectomy is the high nasal carriage-rate of streptococci during or after streptococcal throat infection, and Holmes and Williams find some indication that the non-type-specific immunity which follows exposure to group-A streptococci (whose existence was strongly corroborated by this study) may be impaired when tonsils have been removed. Moreover, type-specific immunity was found to be a significant factor in protection against reinfection under communal conditions, affording considerable protection on re-exposure to the homologous type Some evidence, too, was obtained that type-specific immunity was evoked by exposure without frank clinical infection.

Analysis of spread of infection within the subcommunities studied showed the importance of the introduction of new types of group-A streptococci Reinfection on re-exposure to a given type was rare Consecutive large epidemics were never due to the same type, and where there had been an epidemic due to one type the number of cases observed at a subsequent introduction was roughly inversely proportional to the number in the original outbreak Whether certain types of group-A streptococci are more communicable than others remains undecided It may be significant that the prevalent types showed a rather greater frequency of nasal carriage among both cases and carriers

"Dangerous carriers" are those with heavy nasal infection[15] and Holmes and Williams confirm this In the groups of children studied, the presence of nasal carriers (whether in the incubating stage or convalescent) and the arrival of new children in the community combined to cause continued spread of infection within it The fact that tonsillectomised children provided the majority of such dangerous carriers suggests that tonsillectomy has no place in controlling the spread of streptococcal infection. A much more effective measure is the eradication of streptococci from the throat by adequate penicillin treatment[16] (convalescent carriers were responsible for at least 25% of the secondary cases noted in this study) Much less important are environmental control measures bedding and air disinfection play little part in disseminating streptococci

The detailed analysis to which Holmes and Williams have submitted their data provides many valuable conclusions The underlying lesson perhaps, is that transmission of streptococcal infections is a matter of direct spread from infected individual to individual The most effective transmitter is a person incubating an infection, it probably takes a healthy or convalescent carrier longer to transmit as much

MIDGET ANÆSTHETIC MACHINES

NITROUS oxide is still the anæsthetic most commonly used for outpatients, but sometimes a more potent inhalational agent is valuable Cyclopropane has been recommended for this purpose,[17] and two highly portable apparatuses have been developed to enable a few minutes of surgical anæsthesia to be produced with this agent.

One apparatus, developed in the United States,[18 19] delivers 40% cyclopropane with 30% oxygen and 30% helium It incorporates a very small carbon-dioxide absorption canister of about 100 c.cm capacity, accordingly a closed system of anæsthesia can be obtained for 3–20 minutes This machine is also adaptable for resuscitation with 100% oxygen The other apparatus, of English origin,[20] is more simply designed to give about 1½ minutes' anæsthesia without carbon-dioxide absorption from a mixture of 50% cyclopropane, 25% oxygen, and 25% nitrogen The gases for both machines are compressed in tiny disposable cylinders Helium or nitrogen is necessary to render the mixture non-ignitable

Such simple machines have several advantages they are extremely portable, and they deliver a fixed concentration of gases that is known to produce good, though brief, surgical anæsthesia without hypoxia The safety of a single dose of a high concentration of cyclopropane can reasonably be regarded as established by the many patients who have now been satisfactorily dealt with in this way without major complications[19 21 22]

The title of Sir JOHN STOPFORD has been gazetted as BARON STOPFORD OF FALLOWFIELD, of Hindley Green in the County Palatinate of Lancaster DR STEPHEN TAYLOR becomes BARON TAYLOR, of Harlow, in the County of Essex.

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[11] American Trudeau Society *Amer Rev Tuberc* 1958, 78, 145

[12] *Lancet*, 1958, i, 1163

[13] Holmes, M C., Williams, R. E. O *J Hyg , Camb*, 1958, 56, 43, 62.

[14] *ibid* 1958, 56, 197, 211

[15] Hamburger, M , Green, M J , Hamburger, V G *J infect Dis* 1945, 77, 68, 96

[16] Denny, F W , Wannamaker, L. W , Hahn, E O *Pediatrics*, 1953, 11, 7

[17] Bourne, J G *Lancet*, 1952, ii, 705.

[18] Hingson, R. A *J Amer med Ass* 1954, 156, 604

[19] Hingson, R. A *ibid* 1958 167, 1077

[20] Bourne, J G *Brit med J* July 5, 1958, p 47

[21] Bourne, J G *Proc R Soc Med* 1954, 47, 416

[22] Mushin, W W , Thompson, P W *Brit med J* 1958, i, 1376

Special Articles

EFFECTS OF ATOMIC RADIATION

United Nations Report

The United Nations Scientific Committee on the Effects of Atomic Radiation was charged by the General Assembly with the task of studying and assessing observations supplied by member states on the levels of ionising radiation and radioactivity in man's environment and their effect upon him The committee was established in December, 1955, and the report published this week records the results of a long and intensive study of a mass of information collected from all over the world The text of the report is brief far longer are the detailed annexes which summarise and analyse the technical data submitted to the committee The report represents the most complete picture of the situation yet assembled, and we publish here some extracts from it

The States represented on the committee were Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt (later the United Arab Republic), France, India, Japan, Mexico, Sweden, U S S R , the United Kingdom, and the United States The United Kingdom was represented at the committee's first session by Prof W V Mayneord and at subsequent sessions by Dr E E Pochin

LEVELS OF RADIATION

The committee has estimated the average amounts of radiation likely to be received by populations during specified periods An averaging period of 30 years has been used as relevant to transmissible genetic changes and 70 years as far as somatic injury during the lifetime of an individual is concerned Estimates for medical examinations and occupational exposures were based upon " the present situation in certain countries with developed facilities, rather than on a forecasted world average "

Natural Sources

In certain parts of the world the natural background radiation dose may be as much as ten times greater than the worldwide average and the report points to the relevance of inquiries into the health of people living in such parts in expanding knowledge of chronic low-dose irradiation Harmful effects attributable to radiation from natural sources are not known with any certainty, but, the report adds, it seems likely that some genetic, and possibly some somatic, injury is caused in this way

Medical Procedures

In countries with extensive medical services, the radiation given for medical purposes makes the largest artificial contribution to the irradiation of the population, but no data are available for countries less fully provided with medical resources The reported values of genetically significant doses are of the same order as the doses from natural sources The contribution from diagnostic X-ray examinations greatly exceeds that from radiotherapy and radioisotope applications, and 80–90% of the total diagnostic dose to the gonads is due to relatively few types of examination of the abdomen and pelvis

The significant dose to bone and bone-marrow from medical procedures has been less closely studied than the genetically significant dose, although it may be of importance if bone tumours or leukæmia are induced by low doses of radiation Although individual marrow exposures vary very widely, the average is unlikely to differ greatly from that received by the marrow from all natural sources

Occupational Exposure

Even in countries where occupational exposure is probably greatest it is estimated to contribute to the total irradiation of the population a dose of only about 2% of that from natural sources But, the report goes on, with an increasing use of nuclear reactors and radioactive materials and probably of medical and industrial radiological procedures " this is clearly a figure which should be kept under close review "

Fallout

The committee's estimates for the genetically significant and mean marrow doses from stratospheric fallout of nuclear-test material have been computed from worldwide average deposits The radiation due to stratospheric fallout from weapons exploded so far will contribute, it is estimated, a 30-year gonad dose of 0 010 rem [1] and a 70-year per-capita mean marrow dose of 0 16 rem and 0 96 rem for two populations deriving most of their dietary calcium from milk and rice respectively The corresponding estimated doses from natural sources are shown in the accompanying table For 70-year mean marrow doses, a conversion factor of 14 turns rems into strontium units [2]

Cæsium 137 (^{137}Cs) is responsible for most of the gonad radiation from fallout It becomes distributed more or less evenly throughout the tissues, causing uniform irradiation of the whole body, and when present in the surroundings, its penetrating α-radiation causes a similarly uniform irradiation of tissues

Strontium 90 (^{90}Sr) is not a gamma-emitter and does not contribute significantly to the irradiation of any part of the body from without, but its selective concentration in bone raises problems that do not appear with ^{137}Cs The highest concentrations of ^{90}Sr in bone have been observed in children from a few months to five years old The bone-marrow exposures from fallout shown in the table are due to the ^{90}Sr content of bone and refer to the concentrations estimated for children of these ages

The ^{90}Sr concentration in bone is also affected by dietary habits and agricultural conditions and by the ratio of the amounts of ^{90}Sr to calcium in the diet, and the committee has assembled much useful data on these points The estimates for bone-marrow exposures due to fallout are given for different conditions one based on observations in the United States and the United Kingdom, where milk is the main source of dietary calcium and ^{90}Sr, and where soil calcium contents are commonly high, and the other based on data from Japan where milk products are much less used and where rice and other vegetable products form the main source of dietary calcium and ^{90}Sr and where low calcium soils are common

It is evident, the report sums up, that the exposures from fallout which are most likely to be of significance are

(*a*) Those from short-lived fission products and radioactive material from local or tropospheric fallout

(*b*) Those of the gonads and other organs from ^{137}Cs due to stratospheric fallout

(*c*) Those of bone and adjacent tissue from ^{90}Sr which also comes largely from the stratosphere

BIOLOGICAL EFFECTS OF RADIATION

Present uncertainty about the effects of low dose levels makes it imperative, the report declares, that as much relevant information as possible be collected about groups of persons chronically exposed at these levels and

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[1] Dose in rem = dose in rad × relative biological effectiveness (R B E) R B E = 1 for X, γ, and β rays and 10 for α rays

[2] 1 strontium unit = 1 micromicrocurie of ^{90}Sr per g of calcium

ESTIMATED DOSE FROM DIFFERENT RADIOACTIVE SOURCES

Sources	Genetically significant dose (rem) (Maximum for any 30-year period)		Per capita mean marrow dose (rem) (Maximum for any 70-year period)			
Natural sources	3		7			
Man-made sources (except environmental contamination and occupational exposure)	0·5–5		Ranges beyond 7			
Occupational exposure	Less than 0·06		0·1–0·2			
			Estimates for countries deriving most of dietary calcium from milk		Estimates for countries deriving most of dietary calcium from rice	
Environmental contamination (hypothetical cases)						
Weapon tests cease at end of 1958	0·010		0·16		0·96	
	Assumption *a*	Assumption *b*	Assumption *a*	Assumption *b*	Assumption *a*	Assumption *b*
Weapon tests continue until equilibrium is reached in about a hundred years	0·060	0·12	1·3	2·8	7·5	17

Assumption *a* is that the injection-rate of radioactive material is such as to maintain a constant fallout-rate of ^{90}Sr and ^{137}Cs. Assumption *b* is that weapon tests equivalent in release and stratospheric injection of fission products to the whole sequence of weapon tests from the beginning of 1954 to the end of 1958 will be repeated at constant rate.

for whom adequate control groups exist—for instance, certain populations in areas of high natural radiation and workers in uranium mines. A W.H.O. expert committee has recently been planning such an inquiry, and they have in mind the monazite region of Kerala in India.

Genetic Effects

Exposure of gonads to even the smallest doses of ionising radiations can give rise to mutant genes which accumulate, are transmissible to the progeny, and are considered to be, in general, harmful to the human race. A dose of between 10 and 100 rads per generation would probably be required to double the natural mutation-rate in human populations. Besides increasing the incidence of easily discernible disorders, increased mutation may affect certain universal and important "biometrical" characters, such as intelligence and life-span. Continued small genetically significant exposure of a population may affect not only a correspondingly small number of individuals seriously but also most of its members to a correspondingly small extent. From the genetic facts it studied the committee concluded that exposures to ionising radiation should be reduced wherever possible, and that medical and industrial procedures tending to increase radiation levels to which human populations might be exposed should be carefully weighed as to such benefits or hazards as each may have.

Threshold or No Threshold?

The dose-effect relationship may be of two general types: the effect may be directly proportional to the dose, or there may be a threshold below which no effect occurs. Intermediate relations may be assumed to exist, represented by a curved line, showing extremely little effect at low dose, thus indicating an "apparent" threshold. All studies of the dose-effect relationship are complicated by the unavoidable presence of natural radiations. In man the annual dose from natural radiations is about 100 millirem. It is assumed that a certain amount of genetic damage in man is caused by these radiations; it is conceivable that analogous changes may occur in somatic cells and that such changes, being cumulative with age, may have adverse influences. But there is at present no evidence for such an assumption.

In human adults it is difficult to detect the effect of a single exposure to less than 25 rem, or of continuing exposure to levels below 100 times the natural. Morphologically recognisable damage may be induced by total or partial, continuous or intermittent irradiations much in excess of the currently accepted "maximum permissible levels" of occupational exposure—such damage as leucopenia, anæmia, and leukæmia. As the dose of radiation is reduced below the amounts giving rise to acute functional or morphological alterations, the reactions of the organism become more difficult to detect immediately and the effects may be progressively delayed in time. Thresholds are not easily revealed under these conditions of exposure; in fact, for some of the most delayed phenomena, the report adds, it is uncertain whether they exist. "At the present time, due to the fact that threshold doses for the delayed somatic effects of radiation are not exactly known, it must be recognised that the exposure of human populations to increasing levels of ionising radiations may cause considerable and widespread somatic damage."

ESTIMATES OF CONSEQUENCES

The report emphasises that any attempt to evaluate the effects of sources of radiation to which the world population is exposed can produce only tentative estimates with wide margins of uncertainty. Nevertheless, on the basis of the dose estimates and the available data about likely somatic and genetic effects of given exposures, the committee have tried to evaluate the possible effect of natural and fallout radiation in causing leukæmia and major genetic effects. These estimates indicate only the order of magnitude of the frequency with which effects may be produced, and "our ignorance as to whether thresholds exist . . . cause the greatest uncertainty in the estimates".

Leukæmia

The natural incidence per year in the present world population is put at 150,000, of which 15,000 is attributable to natural radiation. *If there is no threshold* and weapon tests stop this year, fallout radiation may produce an estimated 400 to 2000 cases of leukæmia annually, up to an estimated eventual total of from less than 25,000 to 150,000 cases. *If there is no threshold* and fallout is allowed to reach equilibrium after prolonged continuation of tests, the leukæmia-rate due to fallout may be 5000 to 60,000 cases per year (compared with a natural incidence of 250,000, the world population being assumed to have increased from 3000 million to 5000 million). In another series of calculations the committee assumed a threshold of 400 rem. Under these circumstances the estimates for fallout leukæmia drop to zero, unless individual bone-marrow dose exceeds the mean value by a large factor.

Major Genetic Defects

Assuming a future world population of 5000 million, the natural *annual* occurrence of major genetic defects is put *in the range 700,000* to 3 million cases Of this total, natural radiation may account for 25,000 to 1 million If tests stop in 1958, a total of 2500 to 100,000 cases may arise over subsequent years as the result of genetic damage due to fallout radiation If tests go on to equilibrium the estimate for fallout-determined genetic defects is 500 to 40,000 cases per year

CONCLUSION

In its general conclusions, the committee says that all steps designed to minimise irradiation of human populations will act to the benefit of human health Such steps include the avoidance of unnecessary exposure resulting from medical, industrial, and other procedures on the one hand and the cessation of contamination of the environment by explosions of nuclear weapons on the other "The Committee is aware that considerations involving effective control of all these sources of radiation involve national and international decisions which lie outside the scope of its work" Here footnotes to the report give the text of alternative draft proposals put before the committee by the U S S R and India The Russian view was that the data were sufficient to enable the committee to conclude that there should be an immediate cessation of test explosions This proposal was rejected, Czechoslovakia, U S S R, and the United Arab Republic voting for it and Belgium and India abstaining The Indian wording was "The physical and biological data contained in the report lead to the conclusion that it is undesirable to allow any general rise in the level of world-wide contamination because of its harmful effects and that any activity which produces such a rise should be avoided Nuclear tests are the main source at present which produce such a rise" This proposal was also rejected the voting was 5 for and 5 against, with 5 abstentions At a press conference last week, Dr Pochin said that the Russian draft implied that the committee had considered both the pros and cons of nuclear tests, whereas in fact only the cons had been within their terms of reference

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MANAGEMENT OF CHRONIC PSYCHONEUROSIS IN GENERAL PRACTICE *

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The chronic diseases seen in this practice have been studied over the past fifteen months All the permanent and the frequently recurring diseases are recorded There are some 8000 patients at risk, and about a quarter of them have a chronic disease Sometimes the disease is serious (e g, cancer or tuberculosis), sometimes it is recurrent (e g, asthma or peptic ulcer), and sometimes it is comparatively trivial (e g, a lazy eye or psoriasis) Chronic mental disorders account for 14% of all the chronic patients (see table) This figure does not include the psychosomatic disorders, which account for another 30% of the chronic diseases recorded

Far and away the largest chronic psychiatric problem in general practice are the psychoneurotics, they stem from three sources chronic anxiety, inadequate personality, and unresolved depression These types of case cannot be neatly pigeon-holed under clearcut diagnoses The patients listed show, in many cases, a mixture of two or even all three sources In other words, a patient with inadequate personality who cannot face the stress and strain of life may become anxious or depressed or both, and become permanently disabled Unless the patient was known before he became ill, it is often impossible to pinpoint the cause of his illness

These patients all have symptoms which worry them but have no adequate physical basis Either their condition is permanent or they are so insecure that the least upset bowls them over, and, once ill, they take longer to recover than most people They do not appear to respond to psychotherapy If not constant attenders at the surgery, they are seen much more often than their more stable brethren Some can work, and a few reach a high standard of proficiency in their work, especially the neurotic tidy obsessional housewives Most are inferior workers, doing labouring jobs which they frequently change, absenteeism is rife, and many are permanently unemployed

CHRONIC MENTAL DISORDERS IN A GENERAL PRACTICE

Illness	No of males	No of females	Total
Psychoneurosis	60	104	164 (56%)
Epilepsy	30	26	56 (19%)
Schizophrenia	12	10	22 (7%)
Amentia	12	5	17 (6%)
Alcoholic addiction	9	4	13 (4%)
Senile dementia	4	8	12 (4%)
Paraphrenia	1	3	4 (1%)
Psychopathic personality	4		4 (1%)
Compensation neurosis	3		3 (1%)
Total	135	160	295

When I first went to Ibstock fresh from a neuropsychiatric centre, I was full of enthusiasm and tried to help some of these patients by psychotherapy

Case 1 —Mary was a single woman, aged 40 Her illness started at the age of 16, when spinal disease was diagnosed and she was put on her back for three months Since then she has always had a "weak back", although no general practitioner or specialist has been able to explain the cause. From the psychological point of view she had enough to break anyone's back She was an intelligent and very capable person, but at the age of 14 all hopes of advancement along her own lines went when she was drawn into the family business because of her mother's illness The family were thrifty and hardworking to a degree of absurdity Work and money-making were the only things that mattered Social life was frowned on, smoking and alcohol were forbidden At the age of 40 her mother still referred to her as a young girl and treated her as such

After a few sessions there was a vast outpouring of hatred against her mother, with floods of tears This psychocatharsis helped, but improvement was only temporary For months I saw her periodically for a painful session of half an hour or more She cannot improve, because she is in a hopeless trap until her parents die, and by then it may be too late She has not the training, resources, or courage to go elsewhere She cannot change either herself or her circumstances, and so she remains a chronic and troublesome neurotic

Case 2 —Susan, aged about 42, was coaxed back to work after ten years on the club with a spurious label of thyrotoxicosis She kept at work for a year or more and then relapsed, and I could not get her back to work a second time She now has a certificate for nervous debility

I tried my hand at several such problems, but with none did I achieve any lasting success My senior partner is a first-class physician, but he claims to have no interest in psychiatry Looking back over twelve years, I realise that I have not cured a single chronic psychoneurotic whom he had failed to cure I was able to help some for a limited time, but in the end I was defeated I believe that, with more time, one might be able to help more of these patients, but the hours of work required are quite out of keeping with those available in general practice

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* From a lecture given to general practitioners at the Uffculme Clinic in Birmingham on March 19, 1958

Some timid souls, however, are helped by repeated interviews and reassurance, they come to the surgery at short intervals for maintenance doses of the most simple psychotherapy

Case 3 —Jill is an anxious woman who comes of a neurotic family When her son contracted paralytic poliomyelitis, she developed a pathophobia for herself and her family Any trivial complaint brings her to see me, and I encourage her to do this, because it is usually quite easy to listen to her story, to explain what is happening to her, and to reassure her I do not think that she has the mental capacity for deep therapy, which might make her permanently more secure She knows that I will always listen to her She is better employed getting my opinion than that of the neighbours I never deceive her, we understand each other

Case 4 —Sybil is an attractive young woman, aged 27 She keeps her house like a new pin She has been in trouble ever since I have known her First she fell out with her parents and went to live with relations Then she had trouble at work Her next difficulty was with the landlord of her rooms after her marriage After a year of misery she found a house, and then became depressed because no baby was coming along She conceived soon afterwards, and her pregnancy was the best nine months I have known her to have Indeed she has since admitted that it was the happiest time of her life This island of contentment in a sea of anxiety and depression may be significant She had an easy labour, and then troubles began with a vengeance The baby would not conform, and both the health visitor and I were fearful at times for his life and hers She saw a psychiatrist and electroconvulsion therapy was given, with only a doubtful response She now felt that she was labelled and that the neighbours jeered at her because she had been to a mental hospital "It doesn't matter where I go, I am in trouble What is wrong with me?" she asks I see a great deal of her, and although I seem to be unable to help her radically, she seems to be helped by maintenance doses of understanding, sympathy, and reassurance I am the only person she can turn to in trouble She knows I will always listen to her story, bear with her tears, and in general be a kind of safety-valve

Ideally we like to feel that the psychoneurotic patient will respond to some talking type of treatment, improve, and cease to visit us We aim at helping them over a crisis, so that they can stand unassisted on their own feet This never happens with the chronic patient, talking may help a little but never cures All the rules of formal psychotherapy are broken with this type of case A placebo is often essential, sedation is sometimes useful, and repeated examinations are on occasions unavoidable

One class of psychoneurotic looks to his bottle of medicine as an essential part of life, it is a kind of fetish The colour, constitution, or taste does not matter, so long as it is the same each time He has a kind of "apple a day" philosophy "Three doses a day keeps the illness at bay"

Case 5 —Tom was a man, aged 60, when I first knew him twelve years ago He was off work because of hypertension, but there never has been any evidence that it was really the source of his trouble He has a bottle of the same mixture every two weeks We always have a chat about gardening or grandchildren for five minutes, and then off he goes This is a happy arrangement for both of us I keep him well, he does not waste my time We both enjoy the fleeting contact

A rather more time-consuming patient is the one who likes to have a "check up" each time he calls to see the doctor He has his coat off and his chest bare almost as soon as he comes into the surgery He seems satisfied with the most cursory examination, but just feeling his pulse and looking at his tongue is not enough He is really another version of the chap who must do his quota of press-ups and physical jerks each day to prove to himself that he is still fit I think one must just accept it that the examination is just another form of placebo from which one can never wean the patient A periodic examination of these people is desirable because it is rather upsetting to find that the old neurotic has developed an inoperable growth under one's very nose They all have to die sometime, but it is as well to know when this is imminent

Sometimes a drug helps the patient by easing nervous tension, and many of these patients cannot live comfortably without a sedative, a hypnotic, or one of the amphetamine preparations This appears to do them little harm, and apart from an occasional drug rash I have seen no complications We give phenobarbitone quite freely to epileptics year after year without a qualm of conscience, and they rarely come to any harm True addicts are occasionally found These people depend entirely on the drug, which they take in increasing doses, and withdrawal causes a violent reaction This true addiction must be very rare We in Ibstock have covered about sixty years of practice between us and have never had such an addict on our hands, although phenobarbitone and allied drugs are given frequently to the chronic psychoneurotics Apart from the use of chlorpromazine in chronic or recurrent psychotics, I have found no use for modern tranquillisers I certainly do not feel that anything more useful than amylobarbitone, amphetamine, and phenobarbitone has been produced so far

There is little hope of changing the warped personalities of these people, but one can occasionally ease environmental stress Sometimes a change of work is indicated The hysterical man is often an ambitious fellow who, like many immature personalities, has an exaggerated idea of his own capability He comes to grief trying to work beyond his capacity, and by persuading him to take a less exacting job one often helps him at least for a time Occasionally a new house will make all the difference It is well known how quickly slum dwellers can make a new council house into a pigsty, but this does not always happen, and I can think of families where the new house made a big difference The help of social workers here can be most useful Rotherham, in Yorkshire, was years ahead of most places when in the early 1930s it started and completed slum clearance The rent collectors on the new estate were all social workers who had the skill and tact to advise the new occupants to keep the coal in the coalhouse and not in the bath, and so on, and the scheme worked, and very few slum dwellers did not improve in housecraft

Patients with inadequate personalities respond well to suggestions, especially from a kindly parent figure It is important to establish genuine good rapport and to become a good parent, then, even if they cannot be altered radically, the rates and taxes can be kept down by maintaining them at work as much as possible

Case 6 —When old Dan comes along complaining of pains in his testicles, I know he will have at least a couple of weeks on the club To begin with I bow to the storm, I listen sympathetically to his story, I sympathise, I establish myself in the position of the kindly parent Once firmly in that position I begin to prepare him to go back to work, this awful news must be broken to him gently It should never be "You must start work tomorrow ", but rather " You will be all right by the weekend " In this way Dan is levered back to work, and I suppose he does work for 10 months in 12, which is much better for the community than no work at all

Advice on birth control may help the mother who is already overwhelmed by the size of her family Unfortunately few of this type of patient have the wits or the self-control necessary to use it effectively I tried to induce Sylvia to use a contraceptive sponge I showed her how to use it, but she had a better method She attached tapes to it and wore it like a sanitary towel and has had a further 5 children since I gave her that advice

Depressives

Of all the patients we meet in general practice those who suffer from chronic depression are the most pitiful and, I think, the most trying They have usually seen a long list of consultants whose advice has not helped to solve their problems They may have seen a psychiatrist and had electroconvulsion therapy or refused to have it They are usually not bad enough to be certified, but many have had months in mental hospital with repeated courses of electroconvulsions and even leucotomy, and none of this treatment has helped them They are sick people, tearful, depressed, and depressing They wreck all happiness in the home with their misery and self-pity The general practitioner is left with a feeling " I have tried everything I know with this patient, and nothing helps, and I know of nothing I can do or anyone else can do to help " The chronic anxiety and hysterical state can be jollied along with understanding sedative or placebo Nothing appears to help the depressive, and there is always some risk, albeit small, of suicide So far only one of my chronic depressions has successfully taken his own life Some of these patients are reluctant to see a psychiatrist or to have electroconvulsion therapy If such treatment has not been given it is well worth a trial in these cases, even after years of depression

Case 7.—Martha was aged 36 when I first came across her Her troubles had started at the age of 16, when a young man kissed her, and she was sure she would become pregnant She came to me twenty years after this initial upset, depressed beyond words because she had missed a period She was married and claimed to want children She was not pregnant but she could not be convinced until nine months had elapsed Thereafter, though she agreed that she was not pregnant, she remained a miserable and depressed hypochondriac Talking did not help, and, although she saw a psychiatrist, she refused to have electroconvulsions This went on for five long weary years until her sister-in-law developed a depression The younger woman had electroconvulsion and improved so rapidly that my patient agreed at last to have them Much to my surprise and relief she improved a great deal She is not a robust normal person, but she is a pleasure to handle compared with what she used to be

These patients seem to have no insight into their illness, and certainly no ability to help themselves

Case 8—Ruth was diagnosed as a depressive in 1948 She saw a psychiatrist, who suggested electroconvulsion therapy, but she refused to have it, and she was never certifiable A year or two later signs of disseminated sclerosis emerged and she became even more depressed Euphoria is supposed to be characteristic of disseminated sclerosis, but it was not in her case Again a psychiatrist was consulted, but now it was decided that electroconvulsions were contraindicated by the organic lesion She is seen once or twice every week If a visit is missed, I am usually sent for Never have I known a patient with so many symptoms She is always tearful, wishes she was dead, wants to see yet another specialist, and says that surely there must be some cure for her troubles One day I spent hal an hour trying to explain the organic nature of her spasticity and how sometimes one had to accept a disability I explaine how, if a man lost his eyesight through an accident, he coul never grow new eyes, but he could adjust his life I talked t her about Douglas Bader, and I felt most convinced by all m clever arguments When I had at last finished she exclaimed " Wouldn't it be nice if you could find a cure for me ?" and then she dissolved into tears

Spouses should be allowed to unburden themselve and be encouraged by the knowledge that the doctor a least understands something of their troubles In contradistinction to the patient the spouse often shows remarkable insight This is well shown in the following case

Case 9—Elizabeth, aged 56, has been depressed ever since I went to Ibstock She went to a mental hospital as a voluntary patient and stayed only five days Her husband came to see me after Christmas last year to tell me how she had attempted suicide He had gone to do some shopping and on his return found his wife in the rain-butt up to her neck in water " If I had been going to do it I would have gone in head first," was his summing up " I think she waited on the stool until she heard me coming up the passage and then she stepped into the butt just to try and hurt me, to create a scene " I think he was quite correct in his observation

It is important to spot this depressed type of patient They are very sick people in dire need of sympathy They tend to get estranged from their families, and it is most important for the doctor to remain tolerant and understanding, even if he has little to offer by way of active treatment

Conclusions

The general practitioner should not have to carry the burden of these chronic mental patients alone He has useful allies in the district nurse, the health visitor, the duly authorised officer, and the clergy He should make full use of their help In our village the Townswomen's Guild have a rota of volunteers who befriend and visit all the chronic sick This kind of activity on the part of the community should be encouraged and extended Whether we like it or not, the psychoneurotic will remain on our hands until he dies or we die If we can find ways and means of making our association more useful to the patient, we also make it more tolerable to ourselves This section of the community is often a heavy burden on their doctors Today the fate of the chronic mental-hospital patient is under serious review The chronic mental patient in general practice is also a problem worth a good deal of attention and research

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" Another example of a new plague threatening us now in much the same way as cholera and typhoid used to in the past is injury and death from accidents ! Accident death rates are not actually rising, except among the young men and the elderly, but they are not going down anything like quickly enough, and thus are becoming proportionately more and more important Death and injury by motor vehicles particularly is now very nearly public health problem number one The snag is that it does not lend itself easily to investigation. To begin with, the whole subject is fraught with emotion, people get terribly upset if you start asking them if they drive after having a drink or two (nearly as touchy as when you talk to them about smoking and lung cancer) That is half the trouble about the new plagues in the old days the authorities could remove the pump handle and all would be well In these days it is a matter for the individual *I* have to change *my* habits of eating and drinking or driving or smoking, and that is much more difficult to do than to get someone else to lay on a clean water supply."—Prof E MAURICE BACKETT *Listener*, May 22, 1958, p 839

Occasional Survey

THE FRONTAL LOBES AND HUMAN BEHAVIOUR *

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It is but seventy years since the first observations were published relating changes of behaviour in man to lesions of the frontal lobes (Welt 1887–88) It is true that Harlow (1868) reported the case of a man called Phineas Gage who, after the passage of an iron bar through his head, showed a complete change of personality Both frontal lobes were severely damaged in this man, but the association between the site of the wound and the appearance of the personality changes escaped Harlow, what interested him was the fact that the patient recovered from so grave an injury

Welt's paper forms a definite point of departure, its title—" Concerning changes in character in man following lesions of the forebrain "—is clear and unequivocal Three years later Oppenheim (1890) introduced the term *Witzelsucht*, which persists today as a kind of spurious hallmark of the frontal-lobe syndrome

Many contributions have followed those early papers of Welt and Oppenheim At first based upon the effects of frontal-lobe tumours, cortical degenerations, frontal-lobe injuries, and frontal lobectomies, they have in recent years largely been derived from the study of prefrontal leucotomy and its sequelæ There is still, however, no generally accepted explanation why these frontal-lobe changes take place, and the changes themselves, and the conditions determining their appearance, remain ill defined Moreover, changes in behaviour follow lesions of other areas of the brain, notably of the temporal lobes and the hypothalamus, and it is not yet known to what extent these changes are qualitatively similar to, or different from, those that follow injury to the frontal lobes Bleuler (1951) said " The so-called frontal syndrome is not characteristic of a frontal lesion but occurs also in most other brain lesions if they are localised "

It is certainly surprising to find that, when you have worked at a particular question for years, other observers consider that it does not even exist I think that Bleuler's view is wrong, but the fact that it was possible for him to come to such a conclusion emphasises the present uncertainty

Permanent Frontal-lobe Changes

What kinds of change in behaviour follow lesions of the human frontal lobes ? To answer this question I will draw on the results of an investigation that I made into the intellectual and behavioural changes in 71 men with wounds of the brain (Jarvie 1954a, 1954b, 1956) In 46 of these men the frontal lobes were damaged

The results showed clearly that certain permanent changes in behaviour took place only when the frontal lobes were injured These changes did not take place in every case of frontal-lobe wound, but when they did they often had a particularly destructive effect on the personality They did not appear at all in cases in which damage to a frontal lobe was only slight, and in only 9 of the 37 cases in which it was severe The distribution of these changes among the 9 cases was as follows

Case no	1	2	3	4	5	6	7	8	9
Restlessness	—	P	—	P	P	P	—	P	—
Increased drive	P	—	—	—	—	—	—	—	—
Stereotyped actions	—	P	—	—	—	—	—	—	—
Increased sexual activity	—	—	P	—	P	—	—	P	—
Talkativeness	P	P	P	P	P	P	P	P	—
Inappropriate talk	P	P	P	—	—	P	—	—	P
Impulsive actions	—	—	—	—	—	—	P	—	—
Emotional blunting	?	P	P	—	—	?	—	?	?
Loss of anger response	—	P	—	—	—	—	—	—	—

—, absent, P, present, ?, doubtful

Restlessness

An increase in general activity as restlessness was noted in 5 cases and showed a remarkably consistent pattern the man would move about, to and fro, perhaps following someone, in a way not dissimilar to the quadrupedal pacing after frontal-lobe ablations in the monkey Alternating with the phases of restlessness were long quiescent periods when he stayed in bed

Increased Drive

The restlessness usually made directed activity impossible or difficult, but in 1 case the change in the man's activity took the form of a well-coordinated increased drive, such as has previously been reported after frontal lobectomy (Ackerly 1935, Rylander 1939)

Stereotyped Actions

In the monkey stereotyped actions may be superimposed upon the basic pattern of quadrupedal pacing, the animal, for example, touching a feeding-box over and over again Similar stereotyped actions are seen after wounds of the frontal lobes One man, when given a pencil, began to scribble with aimless repetitive strokes, and it was not easy to stop him, another denuded an area of his skin with repeated scratching

According to Denny-Brown (1952) these limited stereotyped actions seldom persist more than a month after the injury, yet similar actions were noted in 1 man in the present series seven years after he was wounded When interviewed he had attacks of yawning, and he went on yawning as though he could not stop He was also subject to " crazes ", when he would carry out certain actions repeatedly Once it was cleaning shoes " He keeps cleaning all the shoes in the house," said his father, " yet if he went to work in a shoe factory he would soon get tired of it."

Increased Sexual Activity

In 3 men there was an increased desire to carry out the sexual act, and they would solicit their wives persistently for this purpose, both by day and by night With one exception these men made no sexual approach to women other than their wives The exception was a man who had served several prison sentences for indecent exposure This tendency to indecent exposure, like his generally increased sexual desire, only appeared in his personality after he was wounded

Talkativeness

Increased talkativeness was a feature in 8 cases In most of these it simply took the form of a loss of reticence rather than loquacity These men would now butt into conversations, whereas before they were wounded they would have remained silent

In other cases the talkativeness was more obvious, and the man would talk for long stretches at a time There was no sense of pressure behind the talk, and these men could be interrupted, when they would listen quietly to what was being said without attempting to intervene

Inappropriate Talk

In 4 of the men who showed increased talkativeness there was nothing offensive or inappropriate in the content of the talk In the other 4, and in 1 other in whom talkativeness could not be confirmed, the talk was continually, or frequently, inappropriate in one sense or another This inappropriate talk showed many characteristics, being tactless, boastful, hurtful, crude, indiscreet, or sexual Not all these characteristics appeared in each case, but in each man certain dominant themes were apparent

Impulsive Actions

Foolhardy and impulsive behaviour was observed in 1 case.

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* Paper read at a Symposium on the Frontal Lobes held in the University of Liverpool on March 22, 1958

Emotional Blunting

Changes in the capacity of the man to react with normal emotion to ordinary human situations and events proved exceedingly difficult to assess in these cases A few of the men whose behaviour was socially disturbing sometimes appeared to be emotionally unaware of the repercussions of that behaviour on others, but this was by no means invariable This apparent lack of emotional depth was often difficult to reconcile with their emotional warmth in other directions—for example, in their relations with their wives and families In the present series I was able to convince myself of the existence of a real degree of emotional blunting in only 2 cases

Loss of Anger Response

There was complete loss of the normal response to anger-provoking situations in 1 man, it was impossible to make him angry, even by reviling him

Other Changes

Not all the changes in behaviour that were noted after these frontal-lobe wounds persisted as permanent characteristics of the man's personality In certain cases a decrease in spontaneously initiated activity was a striking feature in the weeks and months following the injury, but this might only be perceptible as a slight decrease in initiative years later For example, one man, four weeks after he sustained a bilateral frontal-lobe wound, sat for over an hour with a thermometer in his mouth without raising any objection Within a year he had returned to his former employment, and was so employed seven years later

Emotional attacks, usually of laughter but sometimes of weeping, comparable to what Rylander has called "affective incontinence", normally disappeared within a few months of the man's being wounded, this was also the case with the excessive appetite that was sometimes reported

In none of the frontal-lobe cases was there convincing evidence of a striking, or sustained, elevation of mood, and certainly nothing similar to the spontaneous happiness and jocularity described as euphoria by Rylander (1939) in a high proportion of his cases of frontal lobectomy A few of the men that I examined within a week or two of their being wounded looked euphoric because they had ruddy complexions, appeared exceptionally well, and smiled rather freely In these cases, however, there was no subjective change of mood in the direction of elation, or such change was slight This appearance of well-being was regarded as being due to a temporary stimulation of those autonomic mechanisms that are known to be located in the basal parts of the frontal lobes and the anterior temporal region

Incontinence of urine was not confined to the men with frontal-lobe wounds, but in such cases its incidence was higher, and it was usually present for a longer time than when the wound was restricted to other areas of the brain

Explosive outbursts of bad temper were equally common in cases in which the frontal lobes were injured and in those in which they were not In many instances this explosiveness tended to persist, but it often became less prominent as time went on

Some Explanations

It is difficult to imagine that so diverse a series of changes could ever have been regarded as due to a single cause, yet two explanations of this kind have been put forward to explain the frontal-lobe changes

Scarring

One of the explanations is that the changes are due to epilepsy resulting from the scar that forms after the wound This view was favoured by Hebb (1945, 1949) Hebb and Penfield (1940) described the case of a man with an epileptic behaviour disturbance due to a scar on the frontal lobe whose behaviour was greatly improved after frontal lobectomy

In the present series at least 1 of the 9 men who showed permanent changes of character began to show changes of this type almost as soon as he recovered consciousness, and before any scar could have been formed, and epileptic attacks have not been recorded at any time in 4 of these men since they were wounded In view of this it is difficult to see how these personality changes could be due to epilepsy unless the term is extended far beyond its legitimate usage

Intellectual Deficit

Goldstein (1923, 1936, 1942) considers that damage to the frontal lobes causes a single basic intellectual deficit on which all the subsequent deviations in behaviour depend, the essential nature of this deficit is the loss in the capacity to abstract, in the intellectual sphere this is shown by the inability of the patient to grasp the essentials of a situation, either in a practical everyday setting or in certain special tests—the Goldstein-Scheerer sorting tests (Goldstein and Scheerer 1941) This deficit is not limited to conceptual tasks but affects general behaviour also The patient is able to grasp only part of a behavioural situation, hence his approach to it is faulty, and in consequence he acts inappropriately

It is not difficult to discover from whom Goldstein's views are derived It was Hitzig (1884) who, having confirmed the "silent" nature of the prefrontal areas by their lack of response to electrical stimulation, suggested that they were concerned with "abstract thinking"

The view that frontal-lobe damage causes loss of the capacity to abstract could not be confirmed in the present study All the men were examined with standard intelligence tests, tests that test processes of abstraction to a high degree Of the 9 cases with permanent changes of character intellectual deficits could be demonstrated in only 3, and in 2 of these the intellectual impairment was doubtful

I did not use the Goldstein-Scheerer tests in this investigation, but recent experience of these tests in examining brain-injured people has convinced me that deficits would be demonstrated on them only in cases in which they could also be demonstrated by more conventional tests

It is still widely held that the frontal lobes are intimately concerned with intellectual function Knight and Tredgold (1955) speak of avoiding damage to the "intellectual pathways" in the operation of orbital leucotomy to minimise personality changes Even Rylander (1939) believed, at least in part, that the personality changes were due to some kind of intellectual change He considered that changes such as tactlessness were partly due to euphoria (not a prominent feature in the cases that I have described) and partly due to a "slight blunting in the higher and more differentiated feelings upon which the social and ethical deportment is founded", but he also thought (paraphrasing Goldstein) that they depended "upon a certain intellectual incapacity to adapt oneself to the situation and to correctly appraise how one's remarks are received"

In the cases that I have described many of the men were fully aware of the change in their behaviour, they could give an account of it and were often emotionally disturbed by it It was therefore impossible in these cases to show that the personality changes depended either on emotional blunting or on a lack of intellectual awareness of the changes that had taken place

I know that mental tests are imperfect instruments, and there are aspects of human intelligence that are far beyond their capacity to assess Mental tests are, however, the best means available for measuring objectively human intellectual function If we are going to continue in the belief that the frontal lobes are some kind of special intellectual organ, we must be prepared to find a valid test that will demonstrate these presumed intellectual changes. I think that the word " intellectual " is a bad one to apply to these personality changes, and there are more accurate ways to describe them.

It is clear that there must be some anatomical basis for these changes—some essential anatomical conditions to be fulfilled before the changes appear. Some of the changes, such as the diminished spontaneity and increased appetite, might well be consistent with a general disturbance of frontohypothalamic coordination, and it has been suggested that the restlessness, which is so striking in man and the monkey, is due to damage to the caudate nucleus rather than to the frontal lobe (Davis 1951, Turner 1957).

I do not think, however, that these changes can depend to any great extent on the amount of frontal-lobe tissue destroyed, as suggested by some workers (Frankl and Mayer-Gross 1947, Meyer 1950). In the first place they may not be very obvious even after bilateral frontal lobectomy, and it is clear from recent reports that they are appearing after limited frontal-lobe operations such as cingulectomy and orbital leucotomy (Tow and Whitty 1953, Tow and Lewin 1953).

So far as I am aware, the men that I examined in the present series are still alive, and, in the absence of pathological studies, it is clearly impossible to draw any accurate anatomical conclusions from this material in spite of the excellent radiological and surgical evidence available. The only conclusion that I would draw is that these changes took place, so far as I could tell, in cases in which only one frontal lobe appeared to be damaged, and this observation is consistent with the appearance of similar changes in the few reports of unilateral leucotomy that have been published (Margolis et al. 1952).

Previous Personality

It has long been known that distinctive personality changes follow in only a small proportion of cases with frontal-lobe damage. Feuchtwanger (1923) recognised this when he studied brain-wounded men from the 1914–18 war, and in the cases that I have described personality changes of a distinctive type appeared in only 25% of the men with severely damaged frontal lobes.

Now this is a most significant fact, and I do not think that the explanation of it can be wholly anatomical. It seemed to indicate that the men who developed behaviour changes were in some way different from those who did not, and that the difference might lie in the personalities of the men before they were wounded. Part of my investigation was therefore directed to a study of the normal personalities of the men who showed significant personality changes.

The men had all been brought up in family situations that could well have affected the way in which their personalities developed. Often one parent was dominant, while the other was a cipher. In childhood they were seldom allowed to express opinions of their own, so, when they grew up, they would rarely enter into conversations or assert themselves. " I would walk away rather than get into an argument with anyone," one of them said, " I wouldn't say boo to a goose." They appeared, at least superficially, to be quiet and inhibited in temperament, hence it was not surprising that their parents looked back on them as model children.

It cannot be doubted, however, that conflicts existed beneath the quiet exteriors. These men must often have wanted to rebel against the prohibitions of their environment by making cutting remarks or to overcome a sense of inferiority by boasting—elements that now appear all too obviously in their present behaviour. The man whose talk was almost entirely sexual was preoccupied with sexual matters before he was wounded, although he was regarded by his father as " rather prudish and not interested in sex." The sexual talk was not just talk that happened, not just obscenity, it represented the now open expression of a conflict that was previously concealed.

In these men with damaged frontal lobes certain features in their personalities that were formerly kept under control come to the surface, as though the braking power in respect of these features had become less effective. This was well understood by most of them. " It's out before I can stop it," said one man referring to his tactlessness.

We are all aware of this braking power in relation to our own behaviour. Many of our behaviour patterns are formulated at a subconscious level before they are allowed active expression as speech or other motor acts. These patterns, however, are subject to a process of judgment when their appropriateness or otherwise is assessed before they are translated into action, either completely, or in a modified form. Often it is only after a pattern of behaviour has been executed that we know that it is in some way different from that originally formulated. We are aware, for example, of something that we were about to say but only realise, when we have not said it, that it would not have been appropriate. After frontal-lobe damage certain inappropriate features may be facilitated and gain motor expression before they can be modified.

Now this loss of inhibition is a very characteristic thing and probably depends exclusively on interference with the normal functioning of the prefrontal cortex. It does not extend to every part of the man's behaviour but only seems to occur in relation to those aspects over which the man had to exert a special vigilance before he was wounded, these aspects in turn depending on his personality.

Frontal-lobe Behaviour

I have tried to show that, after lesions of the human frontal lobes, certain striking changes in behaviour take place which are susceptible of explanation.

When I look at this case material again I wonder what I have missed, there remain many facets of frontal-lobe behaviour that puzzle and intrigue me. Why should disinhibition affect only certain aspects of the man's behaviour? Does this mean that we have now to consider different types of frontal-lobe organisation in different people depending on their environmental experiences? Why is so much frontal-lobe behaviour stereotyped and repetitive—not only the isolated stereotyped acts, but also the talk, the sexual behaviour, and the restlessness? Why did the man who had lost much of his capacity for emotional response look so youthful? A youthful appearance was noted by Rylander (1939) in some of his cases of frontal lobectomy. Was it that, being deprived of the emotional repercussions of living, he aged more slowly than we who are continually subject to them?

Today we seek our understanding of brain function among strange arts. We think of it in terms of the mathematical arrangements of nerve-cells (Sholl 1956), or we look for explanations in the working of calculating machines, or in the gyrations of mechanical animals. No doubt the originators of such theories have an ingenuity of mind that few of us possess, but I cannot help feeling that the answers to our questions about the functions of the human brain will not be found in that way but as they have always been found—in the careful collection of clinical facts and their pathological correlations

The investigation upon which this paper is based was carried out during the tenure of a Beit Memorial Research Fellowship, in the department of neurology, The Radcliffe Infirmary, Oxford, and I am indebted to the head of that department, Dr W R Russell, for the facilities received

REFERENCES

Ackerly, S (1935) *Amer J Psychiat* 92, 717
Bleuler, M (1951) *Brit med J* ii, 1233
Davis, G D (1951) D Ph Thesis, Yale University
Denny-Brown, D (1952) *Arch Neuropsiq , S Paulo*, 10, 399
Feuchtwanger, E (1923) Die Funktionen des Stirnhirns Berlin
Frankl, L , Mayer-Gross, W (1947) *Lancet*, ii, 820
Goldstein, K (1923) *Med Klin* 19, 965, 1006
— (1936) *J Neurol Psychopath* 17, 27
— (1942) Aftereffects of Brain Injury in War London
— Scheerer, M (1941) *Psychol Monogr* 53, no 2
Harlow, J M (1868) *Publ Mass med Soc* 2, 329
Hebb, D O (1945) *Arch Neurol Psychiat* 54, 10
— (1949) The Organisation of Behaviour London
— Penfield, W (1940) *Arch Neurol Psychiat* 44, 421
Hitzig, J E (1884) *Arch Psychiat Nervenkr* 15, 270
Jarvie, H F (1954a) *J Neurol Psychiat* 17, 14
— (1954b) M.D Thesis, Glasgow University
— (1956) B Sc Thesis, Oxford University
Knight, G C , Tredgold, R F (1955) *Lancet*, i, 981
Margolis, L H , Simon, A , Bowman, K M (1952) *J nerv ment Dis* 116, 392
Meyer, A (1950) *in* Perspectives in Neuropsychiatry (edited by D Richter) London.
Oppenheim, H (1890) *Arch Psychiat Nervenkr* 21, 560, 705, 22, 27
Rylander, G (1939) *Acta psychiat , Kbh* suppl 20
Sholl, D A (1956) The Organisation of the Cerebral Cortex London
Tow, P M , Lewin, W (1953) *Lancet*, ii, 644
— Whitty, C -W M (1953) *J Neurol Psychiat* 16, 186
Turner, E (1957) *ibid* 20, 216
Welt, L (1887-88) *Dtsch Arch klin Med* 42, 339

Public Health

Chemical Preservatives in Food

THE nutrition panel of the food group of the Society of Chemical Industry met on April 9 to discuss chemical preservatives

Dr M **INGRAM** said that the most commonly used, and at present the most important, chemical preservatives are benzoate, sulphur dioxide, and nitrite All are weak acids, and in each case the undissociated acid is the active preservative, hence, as the pH rises, so does the amount of preservative needed to give an active level in the product All are therefore more active in acid than in neutral substances

Benzoic acid has no odour and no taste and is not volatile, but a fair amount is needed in non-acid materials It is antimicrobial and has no other known effect

The situation is rather more complex in the case of sulphur dioxide The active agent is undissociated sulphurous acid, but, besides dissociation, a series of reversible compounds is formed with sugars such as glucose and other aldehydes (but not with the dissacharide sucrose), greatly reducing the concentration of the active fraction A high limit of 2000 parts per million of sulphur dioxide is set for cordials that are to be diluted A limit of 1500–3000 p p m is set for pulps for jam making, where sulphur dioxide is lost by volatilisation in boiling, the several equilibria in such systems containing sulphur dioxide require time for their adjustment Unlike benzoic acid, sulphur dioxide has other properties—it is a bleaching agent, and inhibits the formation of brown products in food

Nitrite, usually as sodium nitrite, is widely used to cure meat, 200 p p m is the maximum but more may develop naturally from the reduction of nitrate Primarily, nitrite is used to give a good colour but it may have some preservative effect

Sodium diacetate, propionic acid, and sorbic acid have all been proposed for various purposes, but their use is not yet allowed in this country The use of esters has been suggested, but, although many are potent preservatives, they often have pungent odours and are of low solubility

About £10 million pounds' worth of fruit pulp and juice is used in this country in the food industry each year, and storage and transport and handling of this amount of material is rendered possible only by the use of preservatives The attraction of the antibiotics and of atomic radiation is that they may be able to do for the neutral foods what the chemical preservatives have done for the acid ones

Dr J M **BARNES** said that preservatives must by definition be toxic to some forms of life The degree to which they are exposed and qualitative differences in susceptibility account for the death of offending microorganisms while the consumers' tissues escape injury Toxicity tests to evaluate the safety of preservatives must include those assessing the effect of any reaction products formed between the food and the preservative

Benzoic acid has been extensively studied It is quantitatively excreted mostly after conjugation with glycine Up to 4 g has been taken daily by men without ill effect, the margin of safety is therefore very great Sulphur dioxide (or sulphite) has been studied in rats, rabbits, dogs, and man Large doses cause vomiting and abdominal discomfort There is no evidence of any specific reaction to smaller doses

Nitrites, if absorbed, can convert hæmoglobin to methæmoglobin Of the less well-known preservatives, propionates and sorbic acid are metabolised through normal pathways and are probably harmless Borates are undoubtedly toxic and probably cumulative, but the toxicity of formates or formic acid, and of formaldehyde in dilute solutions, is probably much less than has sometimes been assumed

Mr H **AMPHLETT WILLIAMS** cited work by E C Wood which suggests that until a baby is about 6 weeks old it does not produce sufficient gastric hydrochloric acid to inhibit the growth of nitrate-reducing bacteria in the stomach Nitrate *can thus be reduced to nitrite, which can be absorbed with the* formation of methæmoglobin Much water is taken in reconstituted milk, and as little as 30 p p m of nitric nitrogen in the water-supply is now regarded as potentially harmful for infants

Medicine and the Law

Death after Poliomyelitis Inoculation

ON Aug 9 a verdict of death by misadventure was returned by the Manchester City Coroner, Mr G J Pycroft, on a girl aged 2, who had been given an injection of American Salk poliomyelitis vaccine on May 27 and a second dose on July 5[1] The mother noticed no ill effects, but on July 9 the child bumped her head and three days later she died in hospital

Dr Leslie White, the pathologist, said there was no sign of injury but the brain and spinal cord showed acute signs of poliomyelitis infection He did not connect the injections of vaccine with the child's death, because of the time relationship to the fatal illness (the incubation period for poliomyelitis normally being one to two weeks) and because of the absence of any similar incident in other children injected with the same batch of vaccine It was not possible for one dose to be infected and the remainder to be free from infection

The coroner said he must accept the medical evidence, but personally he would have thought there was a strong possibility that the child's death was connected with the second injection of vaccine

Commenting on the inquest,[2] a Ministry of Health spokesman said that the Ministry was not aware that any batch of vaccine issued in this country had proved unsafe Emphasis had always been laid on the fact that vaccination did not guarantee complete protection against the disease Between the start of the vaccination programme in 1956 and the end of July, there had been 35 cases in which poliomyelitis developed within thirty days of inoculation, and with 2 exceptions these were all children During the same period over 6 million children had received two injections of poliomyelitis vaccine

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[1] *Manchester Guardian*, Aug 8, 1958, *Birmingham Post*, Aug 8
[2] *Manchester Guardian*, Aug 9

In England Now

A Running Commentary by Peripatetic Correspondents

"No, George," I said firmly into the telephone "I admit that I often don't know what files are in my In-tray, still less in my Pending, but I've just been down to the Eocene layer—there was a faint outline of an ichthyosaurus between the two bottom files—and I can say with confidence that I have not got your file 'Senior Registrars, beards, long, white, as a distinctive mark of'"

When we met at lunch, George asked if I remembered old MacPrendergast. "When he retired he decided to go through all the files in his trays The bottom one, to his surprise, seemed faintly familiar, and he remembered that when he first joined us he had seen a letter dealing with St. Botolph's Hospital for the Rising of the Lights, and had called for the papers The last patient, he found, had been admitted in 1820 following George IV's coronation, and the Turnover Interval before that had been 17 years Being young and enthusiastic he had decided that, even if no other achievement could be set to his credit during his career in the Department, he would at least close this useless and redundant lazar-house After a bit, of course, he lost interest and anyway was transferred to Establishment, but now it all came back Digging down through the file, he soon passed into the longhand era and farther back to the long *ſ* for s ('*Paſſed* to you *pleaſe*')

"The black letter stumped him a bit but he managed to decipher that Thos Cromwell made it a condition of not being nationalised at the Dissolution that St. Botolph's should also admit cases of the Mother and the Wolf, Tissicks, Purples, and Livergrown, as well of course as Rising of the Lights

"He got quite excited over a 14th-century minute with a date-line 'Januarie 1390' 'Pleynte is made and y-written y-wis that in this maysondewe highte sëynte Botolphe ther be scantness of mete save onlie for the Boarde of Governaunce Chaucer was a Civil Servant, could he have written this himself? But soon he was back to a document on vellum with cheerful little illuminations of Lords of the Treasury and other queer creatures which was a draft reply for the Abbot to put up to the Archbishop suggesting that since Botolph had been a local boy who made good, and since, moreover, a Pædiatric Department had been added as a war memorial after the Senlac '*incident*'—it was politically tactless to talk about the Norman Conquest—the local outcry (*clamitatio vicinorum*) at closure would be so great that the Archbishop might wish to say that the matter was still under consideration. My Lord Abbot inserted the word 'active' (*vivida*) before 'consideration' in the draft but otherwise nothing seemed to have happened. But MacPrendergast wasn't satisfied He had at the back of his mind that there had been earlier letters—much earlier—and that in a moment of depression he had slipped them behind his bookcase There were earlier letters but unfortunately he had put them on top, not behind his bookcase, and, as they were stone tablets cut in runic characters, when he moved the bookcase Well, poor old MacP never lived to draw his pension.

"St Botolph's? Oh, still going strong Of course he never had a hope of closing it Children, and all that And yet they used to say the National Health Service would destroy local interest and patriotism about hospitals!"

* * *

Beyond a vague belief that doctors could not be the only people excused from jury service, I have never known who else shared this privilege or disability with our profession. A wrong address has just brought into my hands a summons to jury duty which includes a "List of Persons entitled to Exemption" It begins grandly enough with "Peers—Judges—Sheriffs—Provosts" (this is a Scottish list) We come near the middle, between "Keepers of Prisons—Professors in Universities" and "Certified Midwives—Officers and men . *on full pay*" (Physicians and surgeons, like advocates near the top of the list, must be *practising*, though oddly enough this does not apply to dentists) The list ends with "Income Tax Commissioners—and Lighthouse Keepers" Truly we are in distinguished company

* * *

I fear that my peripatetic colleague (Aug 2) is overhasty in his condemnation of plastic, for sessional crises were not unknown even before its use

Some twenty years ago, when seats were still substantially constructed in wood, a doctor and his wife went to a dance leaving their small child with a student as a sitter-in On their return they could not find the young woman in any of the ground-floor rooms Rushing upstairs they saw to their immense relief that the baby was sleeping peacefully, but strange noises were coming from the bathroom. The horrified doctor immediately remembered that he had varnished the seat that afternoon and had forgotten to mention it to their visitor

When the door was burst open, it was at once clear that his fears had considerable substance In his best professional manner, he reassured the sobbing and slightly hysterical girl and told her that her freedom was only a matter of moments After two unsuccessful tugs he made a third very powerful heave, lost his footing, fell heavily to the floor, and broke his leg

The situation was now serious, further professional aid was sought in the form of a plumber, who in his wisdom attempted nothing heroic but quietly unscrewed the seat An ambulance was summoned and conveyed the doctor, the girl, and the seat to the local infirmary where they were admitted to the appropriate surgical wards

According to an apocryphal postscript, the house-surgeon felt that he was too inexperienced to deal with such a complicated female case and left her for his chief's operating list in the morning Eventually the anæsthetised patient (seat still in situ) was wheeled into the theatre, and the surgeon, turning to a postgraduate student notorious for his omniscience, said "Have you ever seen anything like this?" "Yes, Sir," was the reply, "Many times, but I have never seen it framed."

* * *

I remember reading about the use of body marks (congenital and acquired) for purposes of identification after some disaster, and I seem to remember, too, that textbooks of forensic medicine dilate upon the subject. But the Police had no trouble at all in identifying a nonagenarian who dropped dead on our Transport Department steps In his pocket was a medical certificate given by me half an hour earlier, testifying that he was fit to drive a car

* * *

As headlines screamed "Paratroops fly into Amman" and "G I s land in Lebanon", I settled down to twenty-one days' terminal leave, probably the most recent "demobee" from the R.A.F In fact, the ink was still wet on my signature agreeing to serve for the specified time on the Reserve of Officers—rather a formality, as I was automatically transferred. Still, I appreciated the polite gesture

Cabinet Ministers drove into Downing Street, through a litter of photographer's flash bulbs, engines warmed up on airfields all over the world, the Navy put to sea, soldiers staggered from Q M stores under mounds of tropical kit, and I arrived home to find an ominous, official, O.H M.S letter waiting for me This was it! No sooner had I managed to get out than they wanted *me* back. By tomorrow I would be swinging on a parachute, dodging noisy bangs from bad-tempered Arabs I squared my shoulders and firmly opened the envelope. If my country needed me to defend the Commonwealth, NATO, the Baghdad Pact, UNESCO, and the Sack Line, who was I to hesitate to answer the call After all, my best blue was still almost new

"Dear F/Lt," I read, "Your Personal Clothing Card Form 667B shows that you were issued with two coats (Coats, White, Medical Officer) on Jan. 23, 1957 Please return same as soon as possible or a cheque for thirty shillings to cover Form 664B action."

Letters to the Editor

CHILDREN IN HOSPITAL

SIR,—Your editorial of July 26, What Hospitals for Children? contains such a burden of special pleading and so many mis-statements in regard to infectious hospitals that it cannot be allowed to pass without challenge First you state that these hospitals are full of children suffering from non-infectious diseases Quite shortly and simply, this is not true Then you complain that they take cases of, " pneumonia, meningitis and gastroenteritis " Why not? Must I remind you that pneumonia and meningococcal infections are notifiable diseases for the reception and treatment of which infectious hospitals were expressly set up and which they are obliged to admit if requested Gastroenteritis too is notifiable in many areas and, in my experience, is sometimes almost as infectious as measles Where else should it go?

Your proposals are certainly drastic and simple You would prohibit the admission of children to adult wards, close childrens' wards in general hospitals, small pædiatric units, and fever hospitals, and decant their contents into a small number of big pædiatric units duly equipped with cubicles which are to be set up at some unspecified date I will not dwell on the arrogant and naive assumption that pædiatricians could take infectious diseases in their stride, but even if they could there are a few practical considerations to be taken into account Normally in my unit, and those I visit, at least half the patients are adults, and if the dividing line be placed at 10 years, the proportion would be considerably higher What is to happen to these patients when the fever hospitals are closed? No doubt the pædiatricians of their charity would be prepared to treat them, but that one feels would be to subject their principles to an unbearable strain

This gibe may sound trivial or unworthy but it serves to underline why so many of us regard pædiatrics as the most artificial of the specialties A small nucleus of genuine *expertise* in the management of the first years of life has been inflated beyond all reason or recognition Thus Dr Lawson (Aug 2) tells us he has 550 beds " fully staffed and equipped to deal with *all* types of cases at all ages from 0 to 16 " (my italics), and makes no bones of his conviction that no other hospital should be allowed to admit cases in that age-group while he has an empty bed Could prerogative go further?

But in any case your proposals represent a retrograde step One of the least disputable advantages of the National Health Service is that it has brought the consultant to the patient even in the remotest village No matter how small the hospital, there is now no difficulty in obtaining the opinion of a neurologist, a dermatologist, a surgeon—or a pædiatrician—as required, and there can be no doubt that this has resulted in vastly improved standards of care Your " small number of big pædiatric units " must be not only few but far between Do you seriously suggest that the parents of a child with whooping-cough or dysentery should have to make a journey of 10 or 20 miles to see him—daily of course? If so, then I am constrained to ask, for whom do you think the hospitals exist—for the public or for the doctors who staff them?

By all means let us have big units for special treatment and facilities for X-ray, better bacteriology and virology with an ever closer liaison between all hospitals, general and special The historical separation of the general from the fever hospital has not been a good thing for either, but there was one particularly cogent reason why the fever hospital was relegated to the nearest mountain top surrounded with a stout high wall—to wit, smallpox And unfortunately that threat still exists, indeed, if air travel continues to become cheaper and speedier so that tours to the smallpox areas become commonplace, importations of smallpox are bound to increase. Then we may have repetitions of what happened in a large London general-cum-fever hospital some time ago There, some 700 beds were put out of action and more than 1000 persons set at risk by a case of smallpox disguised as chickenpox and, had not the disguise been penetrated so promptly and the situation handled so competently, grim consequences might have followed as they did at Brighton in 1951 The question is not so simple as it might appear

The truth is, Sir, that, thanks to convergence of scientific and social factors, the centres of gravity in medicine are changing rapidly as we in fevers know to our cost, our beds in the London area having been cut by 90% since 1939 Pædiatrics, it seems to me, must also cut its coat according to its cloth and grin and bear its cross as best it may Like us in the infectious world, pædiatricians have wrought so well as to imperil their own survival and though this may represent a personal tragedy to many of us, we can scarcely deplore it since undoubtedly from the national point of view it is a matter for rejoicing

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G E BREEN

SIR,—I should like to record my admiration of Professor Illingworth's many years of work on the problems and needs of children of all ages under hospital conditions, problems which he has felt profoundly and now sums up in his lecture to the Central Council for Health Education published in your issue of July 26 His level-headedness in this subject, which has so many emotional undercurrents, is a great asset, as the reforms which his criticisms indicate are the more acceptable, particularly to those with power of administration But I would like to go on to support the plea made by Dr Jacoby (Aug 2) that " daily visiting is not a target to be aimed at but something to be discarded as insufficient for this purpose " particularly, I would add, for the under-fives Sir James Spence told the pædiatric world for many years that mothers were good nurses (not only for babies) The Pickerills at Auckland showed that nursing by the mother reduced cross-infection But although there is widespread acceptance of the truth of these ideas, a general disbelief in their practicability prevails In the pædiatric units of the hospitals of North Bucks (which include an isolation unit) we have nevertheless in the last few years admitted mothers with rather more than half of the children under five Visiting has in the same period gradually become completely unrestricted Professor Illingworth is right to emphasise that we should be cautious about taking a mother away from other children at home, but from the evidence our mothers have supplied and that of other non-psychiatric outside observers, we feel satisfied that the mental health of children left at home has not been jeopardised

When we admit the mother with the child we are in a sense taking on two patients instead of one She also has her needs, as has anyone in strange surroundings and with a worry on their mind These needs must be met by the pædiatric staff who (to borrow a word quoted in your leader from the Royal College of Physicians report) are " attuned " to the special needs of the mothers of sick children This state of attunement of the staff at all levels, above all of the ward sister, comes only by experience built on an initial attitude of accepting the necessity for the mother to be there The magnitude of this need,

or, as some think, its relative unimportance, is one of the main points of controversy at present The need is seen by many to be fundamental for the under-fives, certain over-fives, and any child with cerebral palsy or mental defect who may have to be admitted to hospital Keeping the mother with the child, when properly managed, certainly provides the best solution for the small child's special difficulties and stresses

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[5] Castle W B., Townsend, W E., Heath, C. W *Amer J med. Sci.* 1930, 180, 305

[6] *Lancet*, 1958 i, 1019

[7] *ibid* p 1126

[8] Boyd W Pathology of Internal Diseases London, 1944

[9] Brain, W R. Diseases of the Nervous System London, 1955

[10] Fishberg A M Hypertension and Nephritis Philadelphia, 1954

[11] Becker, B J P *S Afr J med Sci* 1946, 11, 1 97

Letters to the Editor

CHILDREN IN HOSPITAL

SIR,—Your editorial of July 26, What Hospitals for Children? contains such a burden of special pleading and so many mis-statements in regard to infectious hospitals that it cannot be allowed to pass without challenge First you state that these hospitals are full of children suffering from non-infectious diseases Quite shortly and simply, this is not true Then you complain that they take cases of, " pneumonia, meningitis and gastroenteritis " Why not? Must I remind you that pneumonia and meningococcal infections are notifiable diseases for the reception and treatment of which infectious hospitals were expressly set up and which they are obliged to admit if requested Gastroenteritis too is notifiable in many areas and, in my experience, is sometimes almost as infectious as measles Where else should it go?

Your proposals are certainly drastic and simple You would prohibit the admission of children to adult wards, close childrens' wards in general hospitals, small pædiatric units, and fever hospitals, and decant their contents into a small number of big pædiatric units duly equipped with cubicles which are to be set up at some unspecified date I will not dwell on the arrogant and naive assumption that pædiatricians could take infectious diseases in their stride, but even if they could there are a few practical considerations to be taken into account Normally in my unit, and those I visit, at least half the patients are adults, and if the dividing line be placed at 10 years, the proportion would be considerably higher What is to happen to these patients when the fever hospitals are closed? No doubt the pædiatricians of their charity would be prepared to treat them, but that one feels would be to subject their principles to an unbearable strain

This gibe may sound trivial or unworthy but it serves to underline why so many of us regard pædiatrics as the most artificial of the specialties A small nucleus of genuine *expertise* in the management of the first years of life has been inflated beyond all reason or recognition Thus Dr Lawson (Aug 2) tells us he has 550 beds " fully staffed and equipped to deal with *all* types of cases at all ages from 0 to 16 " (my italics), and makes no bones of his conviction that no other hospital should be allowed to admit cases in that age-group while he has an empty bed Could prerogative go further?

But in any case your proposals represent a retrograde step One of the least disputable advantages of the National Health Service is that it has brought the consultant to the patient even in the remotest village No matter how small the hospital, there is now no difficulty in obtaining the opinion of a neurologist, a dermatologist, a surgeon—or a pædiatrician—as required, and there can be no doubt that this has resulted in vastly improved standards of care Your " small number of big pædiatric units " must be not only few but far between Do you seriously suggest that the parents of a child with whooping-cough or dysentery should have to make a journey of 10 or 20 miles to see him—daily of course? If so, then I am constrained to ask, for whom do you think the hospitals exist—for the public or for the doctors who staff them?

By all means let us have big units for special treatment and facilities for X-ray, better bacteriology and virology with an ever closer liaison between all hospitals, general and special The historical separation of the general from the fever hospital has not been a good thing for either, but there was one particularly cogent reason why the fever hospital was relegated to the nearest mountain top surrounded with a stout high wall—to wit, smallpox And unfortunately that threat still exists, indeed, if air travel continues to become cheaper and speedier so that tours to the smallpox areas become commonplace, importations of smallpox are bound to increase. Then we may have repetitions of what happened in a large London general cum-fever hospital some time ago There, some 700 beds were put out of action and more than 1000 persons set at risk by a case of smallpox disguised as chickenpox and, had not the disguise been penetrated so promptly and the situation handled so competently, grim consequences might have followed as they did at Brighton in 1951 The question is not so simple as it might appear

The truth is, Sir, that, thanks to convergence of scientific and social factors, the centres of gravity in medicine are changing rapidly as we in fevers know to our cost, our beds in the London area having been cut by 90% since 1939 Pædiatrics, it seems to me, must also cut its coat according to its cloth and grin and bear its cross as best it may Like us in the infectious world, pædiatricians have wrought so well as to imperil their own survival and though this may represent a personal tragedy to many of us, we can scarcely deplore it since undoubtedly from the national point of view it is a matter for rejoicing

South Middlesex Hospital,
Isleworth, Middlesex

G E BREEN

SIR,—I should like to record my admiration of Professor Illingworth's many years of work on the problems and needs of children of all ages under hospital conditions, problems which he has felt profoundly and now sums up in his lecture to the Central Council for Health Education published in your issue of July 26 His level-headedness in this subject, which has so many emotional undercurrents, is a great asset, as the reforms which his criticisms indicate are the more acceptable, particularly to those with power of administration But I would like to go on to support the plea made by Dr Jacoby (Aug 2) that " daily visiting is not a target to be aimed at but something to be discarded as insufficient for this purpose " particularly, I would add, for the under-fives Sir James Spence told the pædiatric world for many years that mothers were good nurses (not only for babies) The Pickerills at Auckland showed that nursing by the mother reduced cross-infection But although there is widespread acceptance of the truth of these ideas, a general disbelief in their practicability prevails In the pædiatric units of the hospitals of North Bucks (which include an isolation unit) we have nevertheless in the last few years admitted mothers with rather more than half of the children under five Visiting has in the same period gradually become completely unrestricted Professor Illingworth is right to emphasise that we should be cautious about taking a mother away from other children at home, but from the evidence our mothers have supplied and that of other non-psychiatric outside observers, we feel satisfied that the mental health of children left at home has not been jeopardised

When we admit the mother with the child we are in a sense taking on two patients instead of one She also has her needs, as has anyone in strange surroundings and with a worry on their mind These needs must be met by the pædiatric staff who (to borrow a word quoted in your leader from the Royal College of Physicians report) are " attuned " to the special needs of the *mothers* of sick children This state of attunement of the staff at all levels, above all of the ward sister, comes only by experience built on an initial attitude of accepting the necessity for the mother to be there The magnitude of this need, further thought, probably, for the patient's employment and temperament Finally we know that the nephritic hypertensives do worst of all

To seek some arbitrary standard to mark the start of the malignant phase is to betray a total misconception The malignant phase bears no direct relationship with the pressure itself A diastolic reading of 110 may be accompanied by a malignant fundus in an eclamptic young woman, while in a man of sixty a diastolic level of 150 may have produced only the earliest retinal changes

In short, the recognition of individual prognosis amongst hypertensive patients offers one of the supreme clinical challenges of the day We would do well to confess, however, that as yet the power to make this vital discrimination still largely eludes us

Victoria Hospital,
Blackpool

I McD G STEWART

ASPIRIN AND PEPTIC ULCER

SIR,—We are interested in the conclusion of Dr Flint and Dr Allibone (July 2) that aspirin, "although a gastric irritant, is a rare cause of hæmatemesis "

Since September, 1957, 40 cases of hæmatemesis or melæna were admitted to the Burnley General Hospital Each patient was questioned carefully concerning drugs taken during the week preceding the bleeding episode Close questioning was required since many patients habitually take proprietary analgesic preparations and are unaware of an aspirin content of some of these A history of aspirin ingestion within 48 hours of the bleeding was obtained in 20 cases (50%)

During the months of September, October, and November, 1957, when the influenza epidemic afflicted the community with great severity, 16 cases of hæmatemesis or melæna were admitted to this Hospital In the corresponding periods in 1952, 1953, 1954, and 1955, the numbers were 11, 16, 14, and 14 respectively Since a number of medical beds were not in use in 1956 figures for this year are excluded At the time of the epidemic the considerable publicity in the newspapers and on television advocating aspirin-containing preparations for the relief of influenza, probably resulted in a much greater consumption of aspirin than is usual at this time of year

If aspirin is to be incriminated in the production of frank gastrointestinal bleeding, one would have expected a significant increase in the incidence of hæmatemesis and melæna during the epidemic months The figures for 1957 probably represent the true incidence of hæmatemesis and melæna in this area, since the general practitioners would be more than ever likely to regard acute gastrointestinal hæmorrhage as an indication for urgent admission to hospital in view of their very heavy commitments Our experience would lend support to the conclusions of Dr Flint and Dr Allibone

Burnley General Hospital,
Burnley

R E FORGIE
J SHAFAR

WORDS AND THINGS

SIR,—When I was asked whether I had written your admirable leading article on Another Renal Symposium (Aug 2, p 247) I replied with Wilde, " I wish I'd said that," and Whistler, it is well remembered, replied, " Oh, but you will, Oscar "

Your article eloquently concludes " it is not yet certain whether some of the concepts expressed will turn out to be words ('the daughters of earth') or things— 'the sons of heaven' in the round Johnsonian phrase "

The quotation is from the preface to the English Dictionary

" I am not yet so lost in lexicography as to forget that *words are the daughters of earth, and that things are the sons of heaven* Language is only the instrument of science, and words are but the signs of ideas I wish, however, that the instrument might be less apt to decay, and that signs might be permanent, like the things which they denote "

Johnson himself was quoting, and apparently incorrectly, for Samuel Madden (1687–1765) wrote in *Boulter's Monument*, L 377 " Words are men's daughters, but God's sons are things "

I am grateful to you, Sir, for sending me back to Johnson's Preface of which Boswell wrote, " I believe there are few prose compositions in the English language that are read with more delight "

Derby

DOUGLAS HUBBLE

N H.S. STAFF COLLEGE

SIR,—Permit me to thank those correspondents who have replied to my letter either privately or in your columns

I ought to have emphasised that the college would be a meeting place for doctors and their colleagues in the service to talk about people There is no suggestion that administrators would meet administrators and talk about administration Too many exclusive coteries have already been created A new start is proposed to avoid any idea that any one section of our profession or of our lay colleagues is trying to steal a march on the rest

Brighton

W S PARKER
Medical Officer of Health

HOOKWORM AND ANÆMIA

SIR,—May we make some comments on the conclusions of Dr Meiklejohn and Dr Passmore[1] ("   we suggest that a properly financed research project into the association between hookworm and anæmia is now overdue ")?

The view[2-5] that there is seldom a relation between the degree of infestation and the frequency of anæmia in a population was restated in your columns by Foy and Kondi[6] and Trowell[7] on the basis of their experience in India and in Uganda But in particular local situations of infestation, of temperature, and of humidity[8] hookworm infestation is almost constantly associated with severe anæmia, and there is also clinical and experimental evidence that the *Ancylostoma duodenale* first described by Dubini[9] in Milan in 1843 can give rise to a well-defined type of anæmia

So we agree with Foy and Kondi[6,10] that "   although hookworm may play a part in the genesis of the tropical microcytic anæmias, this is probably not a paramount one " because certainly not all the microcytic anæmias of tropical countries may be referred to *A duodenale*, or better to the worm by itself We also agree with Roche[11] that " the role of hookworm in the genesis of some tropical anæmias is probably a paramount one "

A basis for agreement may be found in the proposition that some at least of the tropical microcytic anæmias are primarily due to hookworm infestation

Why does *A duodenale* only exceptionally exert its power to produce anæmia? Recent work on pathogenesis[4,12-14] indicates that deficiency of iron is an essential factor in the production of anæmia Anæmia appears only when the hookworm is able to induce a severe iron deficiency, either by itself or with the help of other influences Without sideropenia, and whatever the degree of infestation, no anæmia develops

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1 Meiklejohn, A P., Passmore, R *Lancet*, 1958, i, 857
2 Tibaldi, E Elmintiasi Intestinal Pavia, 1923
3 Fülleborn, F *Arq Dep Nac Hig* 1927, 33, 35
4 Cruz, W O *Mem Inst O Cruz* 1934, 28, 391, *ibid* 29, 263, 487
5 De Langen, C D *Inde*, 1934, 23, 135
6 Foy, H , Kondi, A *Lancet*, 1956 i, 423
7 Trowell, H C *ibid* p 964
8 Perroncito, E *La malattia dei minatori al S Gottardo ed al Sempione.* Turin, 1909
9 Dubini, A *Ann Univ Med Chir* 1843, 106, 5
10 Foy, H , Kondi, A *Lancet*, 1956, ii, 95
11 Roche, M *ibid* 1956, i, 965
12 Lanzza, P , Ventura, S L'anemia da anchilostoma studio patogenetico Pavia, 1950
13 Lanzza, P , Ventura, S *Hæmatologica*, 1953, 37, 873
14 Lanzza, P , Ventura, S *Sci med Ital* (in the press)

did not realise that Becker had listed another 33 cases under a different heading in an earlier article We regret having failed to quote all Becker's cases, but we consider the important point to be that Becker agrees that " on occasion the Bantu can and does develop just as much atherosclerosis as the European in South Africa " We consider his estimate of the incidence of apoplexy to be too low and would agree with Walker and Simson's figure [7] of 3–4% for the Bantu in Johannesburg We cannot agree with Walker's statement [12] that only 19% of Bantu show aortic atherosclerosis at necropsy

In regard to the points raised by Mr Walker and Dr Simson we omitted to mention coronary disease in our article [13] because we intend to devote two further articles to this problem An early note on our views appeared in your columns last year [14]

Much of the misunderstanding which has arisen regarding the Bantu is due to the fact that his relative freedom from myocardial infarction has been attributed to a freedom from coronary atherosclerosis It must be remembered that coronary thrombosis is only one of several manifestations of coronary-artery disease The Bantu does suffer from coronary atherosclerosis and his myocardium also suffers For example, in hypertension (a very common disease in the Bantu) Becker [11] stated " the coronary vessels are frequently diseased and the myocardium is frequently gravely damaged " And Higginson and Pepler [15], comparing Bantu with Americans and Danes, stated " our observations suggest that severe atherosclerosis of the aorta and coronary arteries are less frequent in the hospitalised Bantu of Witwatersrand than among the American and Danish hospital patients *but the differences are not conclusive* " (our italics)

J D WOODS
W LAURIE

Edendale Hospital,
Pietermaritzburg, Natal

HAZARDS OF CHLOROTHIAZIDE THERAPY

SIR,—I was glad to see the letter by Professor Rosenheim and Dr Ross (July 26) in which they drew attention to hazards of chlorothiazide (' Saluric ') therapy

In common with others I have often found that chlorothiazide leads to an increased loss of potassium in the urine, and the danger of a cellular deficiency of potassium developing in patients who are receiving this drug is therefore very real As is well established such depleted tissues function less efficiently In particular impaired renal function may ensue and digitalis is less well tolerated and a therapeutic dose may also be a toxic dose a potassium-depleted myocardium moreover is subject to arrhythmias Thus the maintenance of adequate digitalisation becomes more difficult and as a consequence the heart-failure may worsen [16,17]

The serum level of potassium is unreliable as an index of body content [18–20], normal or even raised levels may occur in the presence of cell deficiency Moreover, whilst it appears very likely that a low level does nevertheless indicate a cell shortage, in our experience such levels are not often found in congestive cardiac failure In a series of over 450 patients in congestive cardiac failure, under the care of Dr O Brenner, that I studied, lowering of serum-potassium was rare These patients were receiving diuretics other than chlorothiazide, but to date our experience with chlorothiazide is identical It is likely that when the serum level of potassium is low, the cellular shortage is very profound

However, I would like to reinforce their emphasis—namely, that potassium depletion cannot easily, if at all, be diagnosed in the outpatient department let alone in general practice The diagnosis cannot be made on clinical grounds, nor are there simple tests that may be performed to assess its presence

It is, therefore, necessary routinely to supplement with potassium the diet of every patient having chlorothiazide A supplement of about 60 mEq per day is adequate But potassium salts are unpleasant to take and may occasion nausea, vomiting, &c [21] This must be appreciated since there is a real possibility of patients discontinuing their supplements unknown to the doctor It is helpful, in this connection, to see which of the many salts of potassium that may be given are most acceptable to each patient I have used potassium chloride, potassium bicarbonate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, potassium citrate, and potassium effervescens * Other salts have been used in hospital practice, but cannot be obtained easily in general practice These salts are best taken in solution and the tablets of potassium effervescens may be dissolved in water I have found it helpful to give potassium chloride in concentrated grapefruit juice The amount of each of these supplements to contain approximately 60 mEq of potassium is as follows

Potassium supplement	*Amount containing 60 mEq.K (approx)*
Potassium chloride	4 2 g
Potassium bicarbonate	6 6 g
Potassium dihydrogen phosphate	8 2 g
Dipotassium hydrogen phosphate	5 2 g
Potassium citrate	6 5 g
Potassium effervescens †	22 tablets

C T G FLEAR.

Department of Experimental Medicine,
Cambridge, and Queen Elizabeth
Hospital, Birmingham

DIASTOLIC PRESSURE AND MALIGNANT HYPERTENSION

SIR,—In his letter of July 26 Dr Cruz-Coke maintains that by measuring diastolic blood-pressure levels against a standard scale, adjusted for age and sex, it is " possible to identify patients with malignant hypertension before changes are evident in the fundus and before left ventricular hypertrophy develops It also allows the significance of high blood-pressure to be assessed in old people "

These are large claims If we could learn to pick out in advance those patients in whom hypertension will sooner or later go to the bad, in consequence of fatal or disabling vascular damage, we could then treat them with the new autonomic paralysing drugs in the assurance that we should be doing much to avert their destined fate

Unfortunately the criteria suggested by Dr Cruz-Coke are not enough We all know that raised arterial pressure in a young man presents a threat much more serious than the same pressure in an old lady But we still can foretell very little of individual fortune among the members of parallel groups We know, for example, that out of 10 fifty-year-old men with diastolic pressures of 130 mm Hg 2 or 3 will probably be dead in a year or so of strokes, heart-failure, or malignant renal change But we do not know which 3 Another 2 or 3 may very well survive into old age Again we are unable to identify the lucky ones And Dr Cruz-Coke's tables cannot help us

Nevertheless we can bear in mind some points that will enable us to make a rough selection This, in fact, is what we do, almost subconsciously, when we first assess a new patient with hypertension Together with age and sex we certainly consider also the factors of heredity, lability of pressure, and the trend over a period adopted by its resting level, with a

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12 Walker, A R P *Brit med J* 1958, i, 1060
13 *Lancet*, 1958, i, 231
14 *ibid* 1957, i, 1091
15 Higginson, J, Pepler, W J *J clin Invest* 1954, 33, 1366
16 Fletcher, E, Brennan, C F *Brit Heart J* 1958, 20, 204
17 Lown, B, Levine, S A Current Concepts in Digitalis Therapy London, 1955
18 Moore, F D, Edelman, I S, Olney, J M, James, A H, Brooks, L, Wilson, G M *Metabolism*, 1954, 3, 334
19 Burrows, B A, Ross, J F *Boston med Quart* 1956, 7, 54
20 Flear, C T G, Cooke, W T, Quinton, A *Lancet*, 1957, i, 548
21 Flear, C T G, Hill, M, Thomas, G *ibid* 1950, i, 1190

* Now listed in Martindale's *Extra Pharmacopœia*

†		
Potassium bicarbonate	26 56	g per 100 tablets
Tartaric acid	16 87	
Citric acid	11 25	
Sucrose	9·40	

Granulated on a hot plate

We should like to draw attention to the following features

(1) Without exception the psychotic reactions occurred in a labile premorbid personality with strong emotional conflicts preceding the onset of the psychosis In 2 of the cases physical exhaustion was also present.

(2) Physical and neurological examinations including lumbar puncture did not reveal any abnormalities Repeated electroencephalography gave a normal record in 3 patients The tracings of the 4th were abnormal, but inconclusive Therefore, we failed to demonstrate clinical or electroencephalographic evidence of a correlation between the acute psychosis and a presumptive encephalitis

(3) 3 of the 4 patients were young people under 17 The clinical picture was characterised by a confusional state with psychomotor restlessness, delusions, visual hallucinations, and aggressiveness The acute psychotic symptoms cleared spontaneously on the average within two weeks A short-term relapse of the psychotic incident was observed in a single case whose final outcome was also favourable

(4) On the psychodiagnostic level all patients were found to be of normal intelligence with clear evidence of a disturbance of mental equilibrium No support could be found for the assumption of structural damage to the brain, nor of an acute manifestation of a latent psychosis, with the illness in the role of a trigger Rather do we incline to interpret the psychotic episode as the reaction of a personality lacking full integration, maturity, and flexibility to the disturbance of somatopsychic homœostasis caused by the attack of influenza

Talbieh Psychiatric Hospital,
Jerusalem

A A. Weiss
M Kaffman
H Z Winnik

NO MORE NEOLOGISMS?

Sir,—Why not "No More New Words?"?

Chesham, Bucks FFRANGCON ROBERTS

Sir,—In reply to the letters by Dr Pappworth and myself (July 26) you rightly emphasise that an editor has a duty to his contributors, and thus you justify the use of new words which we think are often unnecessary and nearly always serve to obscure But, Sir, has not an editor a duty to his readers, and is it not important that the reader should understand what the writer is trying to say? If the reader cannot understand, why should the author bother to write, or the journal to print, the paper?

You allude to the centenary of the hypothesis of natural selection If I remember rightly, the key to that hypothesis was the elimination of the unfit In this context the unfit are words, and our plea is that the unfit should be eliminated by editorial action.

Oxford. GEORGE PICKERING

"EXPERIENCE AND INCENTIVE" AWARDS?

Sir,—I have read Dr Evans' letter last week with interest, but I would like to suggest a more practical basis for administering awards for meritorious work in general practice

The doctor would apply to the awarding authorities in confidence, giving specified credentials such as 7 to 8 years in general practice (at least 5 as a principal) and a National Health Service list above an accepted minimum varying with districts The censors would then visit him (one hopes unexpectedly) and inspect, they would demand a definite standard of work, surgery premises, equipment, organisation, and note-taking Another censor would sit in during a surgery (this time by arrangement), a third would go on visits with him, and yet another (one hopes over coffee) sound him out to see that his basic medicine is still intact, and that he has made attempts to keep up to date If there is a doctor able to stand up to all this, then he is worthy of the encouragement of an award, and even our most modest colleagues might come forward if they knew that their recognition would in honour bound be kept silent

Who would our censors be? Presumably they would be chosen from our most capable practitioners, stiffened by consultants with examining experience It would be understood that our regional examiners would never examine within their own areas

There is one plea I would put forward, and that is that if a doctor fail to reach the required standard he should be told why, and permitted to reapply after a suitable interval without prejudice

London, S.E.3 L I NORMAN

CONGENITAL FIBROELASTOSIS OF THE ENDOCARDIUM, NUTRITIONAL HEART-DISEASE, AND MYOCARDIOPATHY OF UNKNOWN ORIGIN

Sir,—Johnson[1] suggested that congenital endocardial fibroelastosis is caused by anoxia of the endocardium One mechanism by which this may occur is premature closure of the foramen ovale which prevents blood circulating through the left side of the heart in utero Since the endocardium derives its blood-supply from the blood within the heart chamber it is the site that is predominantly affected It would seem reasonable to consider, therefore, whether anoxia could play any part in the production of endocardial fibrosis of adults

One way in which this could occur would be stagnation anoxia of the blood within the heart chambers It is characteristic of so-called nutritional hearts that they are markedly dilated and pulsate so poorly that they resemble pericardial effusions In such a quiet heart stagnation of blood might well be expected to occur Furthermore, one would expect the site most severely affected to be the apex of the ventricle, and this is where the earliest signs of fibroelastosis are usually found

Two investigations would help to clarify the part played by such a mechanism Retrograde aortic catheterisation could compare the oxygen saturation levels of blood samples taken from the aorta and from the region of the apex of the left ventricle Angiocardiography could demonstrate incomplete emptying of the heart in systole, and how long the opaque material stagnates within the ventricles

It could be contended that all dilated hearts should show a similar change This is not necessarily so, because cardiomegaly from other causes is not usually associated with the quiet almost motionless heart seen in nutritional heart-disease and myocardiopathy of unknown origin. Active contractions, even if not associated with complete emptying of the heart chamber in systole, may be enough to maintain a turbulence that prevents a layer of stagnant blood forming over the endocardium

If stagnation anoxia is a significant factor then fibroelastosis and thrombosis become secondary changes The primary disturbance would be cardiac dilatation, the cause of which remains obscure. Such an explanation would serve to bring these myocardiopathies into much

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[1] *Arch Path* 1952, 54, 237

What are the morphological and biochemical characters of anæmia induced by hookworm? Hookworm produces a typical iron-deficiency anæmia In this conclusion we agree with all who have studied the disease in Italy [15–19] or in other countries (Jugoslavia,[20] France,[21] Portugal,[22] Egypt,[23] Guadalupe,[24] Japan,[25] Brazil [4,26] Of course when other factors are present—either internal (deficiency in production of intrinsic factor, changes in intestinal bacterial flora, production of *infection or infestation, hepatosplenic abnormalities, &c*) or external (deficiencies in B^{12} and folic acid in the diet)—the anæmia may differ from pure iron-deficiency anæmia Though such associations are common in tropical countries, they are exceptional in Europe where ancylostome anæmia is usually of classical iron-deficiency type

Our study of more than 100 anæmic patients brought out these features of hookworm anæmia

(1) Microcytic hypochromic anæmia with red hyperplasia of the bone-marrow caused by inhibition of maturation in the erythropoietic tissue [13,14]

(2) Hyposideræmia (serum-iron under 50 µg per 100 ml) [13,18] hypertransferrinæmia (plasma-transferrin above 350 µg per 100 ml [13,27]), and hyperprotoporphyrinoglobulia (free-erythrocyte-protoporphyrin-9 above 100 µg per 100 ml) [13,28,29]

(3) Intravenous ^{59}Fe is distributed in the typical "iron-deficiency pattern" [14,30]

(4) Constant and quick response to iron therapy [13,14]

Our investigations into other possible ways in which anæmia could be produced, such as excess hæmolysis, or bone-marrow inhibition by hookworm toxins, have clearly shown that hookworm anæmia [13,14] is not determined in any of these ways

The correction of the anæmia by the simple administration of iron, while infestation is still present, is the chief evidence that the anæmia depends exclusively on iron deficiency

The most important question is how the hookworm induces iron deficiency Hookworm may impair the normal gastroduodenal processes by which food iron is dissolved and ionised [14,30] It may also interfere with iron absorption by the duodenal and jejunal mucosa [14,30] *A duodenale* also increases the elimination of iron from the gut by bleeding from mucosal lesions Basing our opinion on our experience with the radioactive method of Gerritsen et al [31] we believe that, *though hæmorrhage, and consequent loss of iron is* very important in the genesis of the sideropenia, hæmorrhage cannot by itself explain all the anæmias in those infested by parasites Severe anæmia may develop in patients with slight blood-loss, and some men with ancylostomiasis may lose about 10–20 ml of blood a day without becoming anæmic

The effect of hookworm may be enhanced by a diet extremely poor in iron or by a diet abnormal in calcium and phosphorus content Such an alimentary factor is of very little significance in Italy and probably in other European countries In other parts of the world, however, [4,32] it is of fundamental importance in the production of iron deficiency The size of iron stores is also relevant, and the exhaustion of these reserves, the first step in the development of anæmia is obviously more easily accomplished in patients with initially low reserves

It is usually a combination of these factors, and not one alone, that explains the development of anæmia in ancylostomiasis We conclude that hookworm anæmia is a real well-defined clinical entity due to iron deficiency induced by worm infestation

Department of Medical Pathology,
University of Cagliari,
Italy

PAOLO LARIZZA
SANDRO VENTURA

SHOULD BIBLIOGRAPHIES GIVE TITLES OF PAPERS?

SIR,—Mr Patey (July 19) has expressed what is a growing concern at the wilfulness of British publishers in not allowing their contributors to provide the title of papers in their references In your own case, the argument is perfectly valid—they would replace a short article *In other journals, and in many English books, the same* practice prevails even when half a page is left blank at the end of an article or a chapter

Now that "the English literature" enjoys a prestige as great as that of "Eng Lit" it is surely mandatory that *it should* be given a final veneer of completeness I suggest, therefore, that *The Lancet* makes the gesture—how I cannot suggest Pressed as you are for space, it is a question of quality versus quantity

Department of Pathology,
Jackson Memorial Hospital,
Miami, Florida

MAX MILLARD

REAPPEARANCE OF TABOPARESIS

SIR,—I have just returned from a two months' guest lectureship in Munich, and I can confirm Dr Noel Harris' remarks (Aug 9) from my observations at the Universitaets-Nervenklinik At least four recent cases of general paresis of the insane were admitted during my presence Syphilis of the central nervous system had apparently not become as rare in the large German cities as it was here, but the recent increase in patients suffering from taboparesis has been noticeable It was thought to be due to the turmoil and strife of populations in Europe after the late war when treatment of venereal disease was inadequate or lacking

Department of Experimental Psychiatry,
The Medical School,
Birmingham

W MAYER-GROSS

NEUROLOGICAL COMPLICATIONS OF ASIAN INFLUENZA

SIR,—In your issue of July 5 you published four interesting papers dealing with the neuropsychiatric complications of Asian influenza In your accompanying annotation you state that psychotic outbursts related to influenza "are a symptom of encephalitis and do not represent a latent psychosis which has been revealed by a generalised infection"

Following the epidemic of Asian influenza in Israel during November and December, 1957, 4 patients who developed psychotic manifestations during the course of the influenzal illness were admitted to Talbieh Psychiatric Hospital, Jerusalem The psychosis appeared in 3 of the cases within three days of the onset of the influenza The correlation between the *development* of the psychosis and recent infection was ascertained by a progressive rise in titre of the hæmoagglutination inhibition for the Asian virus variety during the psychotic outburst (A detailed report of our cases was recently published in *Dapim Refuim*, Israel, 1958)

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15 Benetazzo, B, Gambini, C *Arch ital Sci med trop Parass* 1950, 31, 442
16 Cannavo, L, Caruselli, M L'anchilostomiasi I Congr Studio Mal Inf Parass Rome, 1949
17 Del Zoppo, R *Ann Ig* 1952, 3, 24
18 Giromini, M, Granati, A Anchilostomiasi ed idatidosi nei lavoratori agricoli, xix Congr Med Lavoro Rome, 1953
19 De Maria, B, Rossi Espagnet, A *Rass Fisiopat clin terap* 1957, 29, 923
20 Nikolic, J, Weiser, J *Arch za Higijenu Rada*, 1950, 1, 25
21 Bonnin, H, Moretti, G F *Pr Méd* 1950, 58, 158
22 Trincao, C, Parreira, F, Gouveia, E, Franco, A *Rev Hémat* 1952, 7, 575, 580
23 McFadzean, A J S, Wong, C C *Trans R Soc trop Med Hyg* 1952, 46, 674
24 Languillon, J, Mauzé, J *Sang*, 1950, 21, 652
25 Baba, T, Nagata, K, Aizawa, T *Gunma J med Sci* 1956, 5, 281
26 Cruz, W O, De Mollo, R P *Blood*, 1948, 3, 456
27 Ventura, S *Hæmatologica*, 1954, 38, 227
28 Ventura, S, Meduri, D, Dori, A, Filipazzi, A *Hæmatologica*, 1954, 38, 747
29 Larizza, P, Ventura, S *Sang*, 1956, 27, 610
30 Ventura, S, Marmoni, U, Puricelli, G, Suardi, L, Maioli, G *Hæmatologica*, 1957, 42, 563
31 Gerritsen, T, Heinz, H J, Stafford, G H *Science*, 1954, 119, 412
32 Smillie, W G *Mon Rockefeller Inst med Res* 1922, 17, 73

to interfere with his everyday life and work His cheerily shouted ‘ hullo ’ used to echo round the blocks as he made his daily visits Only a week before his death he attended the staff club’s horticultural show and made one of those speeches which were always so apt and for which he had a justified reputation Staff and patients alike have lost a real friend.

“ For the last twelve months of his life he held the posts of master of the Worshipful Company of Girdlers and renter warden of the Worshipful Company of Inn Holders The former office was held by his late father thirty years earlier He was unmarried, and in all his work he enjoyed the active interest and support of his mother ”

WILLIAM HENRY CASSWELL SPOONER

M.B Lond

Dr W H C Spooner, of Blandford, Dorset, was drowned at Brest on Aug 1 when his yacht *Remarie* was rammed and sunk at her moorings by a tug His wife and three children, who had joined him a few hours earlier, escaped

He was educated at Epsom College and qualified from St Mary’s Hospital in 1932 After holding house-appointments at St Mary’s and at St James’ Hospital, Balham, and an assistantship in North Wales, he went into practice at Blandford, where his greatgrandfather, grandfather, and father had practised before him. During the late war he served in the Royal Air Force

R Mac K writes

“ Spooner was very modest about himself but he was a very good doctor indeed He looked forward all the year to his summer holiday, for the last ten years he took his family cruising in *Remarie* on the Brittany coast. ‘ Skip ’ was a good navigator and knew the coast well Often his was the only yacht among the fishing boats in the anchorage Last week when, after a week with two companions, he reached Abervrach, he said he was happy to be back on this coast He was a good painter in water colours and oils and played a great part in the Forum Club at which professional and amateur artists of Dorset met at Blandford. He was an excellent host Conservative in his outlook, he was open-minded and could admire the Teddy boys for the originality of their dress Perhaps this was just an illustration of his most thoughtful and courteous way with every one of us He will be very much missed and not only in Dorset ”

A memorial service for Sir Arnold Stott will be held in Westminster Hospital’s Chapel at noon on Thursday, Sept. 25

Appointments

BALLANTYNE, J C , F R.C S , D L O E N T surgeon, Royal Free Hospital, London

CONNOLLY, R C , F R C.S neurosurgeon, accident unit, Royal National Orthopædic Hospital, Stanmore.

ORTON, PEGGY K L , F R C.S , D L.O E N T surgeon, Elizabeth Garrett Anderson Hospital, London

PINKER, G D , M B Lond , F R C.S E , M R C.O G consultant obstetrician and gynæcologist, Samaritan Hospital and St Mary’s Hospital, London

SPENCER RALPH, M.B Manc , F R C.S E assistant radiotherapist, Liverpool Radium Institute

VAN WIJK, P J , M B W’srand radiological registrar, Papworth and Addenbrooke s Hospitals, Cambridge

WEMYSS, CAMERON, M B Edin , D P H group medical superintendent, Victoria Hospitals, Glasgow

Manchester Regional Hospital Board

GUYER, O K. G , M.D Edin , M R C.P.E. consultant geriatrician, Preston and Chorley group of hospitals

LEES, V T , M B Manc , D O M S consultant ophthalmologist, Wigan and Leigh group of hospitals

POPHAM, R D , M B Lond consultant pathologist, Bury and Rossendale group of hospitals

WADE, E G , M D Manc , M R C.P consultant cardiologist, jointly with the United Manchester Hospitals

Notes and News

ACCIDENTS TO CHILDREN

ACCIDENTS have now become the leading cause of death among children both in the United States and in Europe At a seminar held at Spa last month by the World Health Organisation it was pointed out that children must not be overprotected, and should be taught to cope with dangerous situations, but at the same time unnecessary dangers should be removed.

In different countries the prevailing risks differ Drowning is particularly frequent in Scandinavia, the Netherlands, and France In Spain, small children lose their lives or are seriously injured by falling into open braziers—a danger that is gradually disappearing as housing is modernised “ A similar problem exists in the British Isles, where the open fireplace is the usual way of heating the home ” In Italy and Poland, damage from explosives left from the last war is a prominent hazard, which vigorous propaganda has done much to reduce Poisoning of young children is common in the U S.A , Switzerland, and Sweden—countries where many chemicals are to be found in the home Suffocation of small children who, while playing, put their head into a plastic bag is reported as a real danger in France, Belgium, Denmark, and Sweden

“ Small children do not understand dangers and must be protected from them, particularly from life-threatening hazards, but as they grow older they must be taught to cope with dangerous situations They must learn to climb, to jump and to fall, to handle knives, forks and scissors, to swim, to use matches and understand fire, to get along in traffic. The wise parent will thus protect the child as far as ever possible from dangers from which the child can learn nothing and not worry about small accidents from which the child can learn how to avoid them It is through this positive approach combined with the elimination of deadly hazards from the environment of the child that it will be possible to reduce the number of accidents ”

ROYAL MEDICAL BENEVOLENT FUND

DURING 1957 this Fund disbursed £43,942 in grants and annuities The number of cases (398) helped by grants was almost the same as in the previous year, but the grants rose by £2599 Though the number of annuitants decreased by 6, annuities amounting to £12,406 (£455 more than in 1956) were distributed. “ This increase in the amount of grants and annuities to approximately the same number of beneficiaries appears to reflect the rise in the cost of living, and the Rent Act, of course, has made its expected impact This may well become more pronounced in 1958 ” The number of people who benefit is much larger than the number of cases quoted Many of these include married couples, children requiring sustenance and education, and widows with families

In his report for the committee of management, Dr T Anwyl-Davies, the hon secretary, asks for more help in meeting demands which, in spite of the Welfare State, are ever expanding

“ To increase our income, new subscribers are essential We are very grateful to those who subscribe annually and we appeal to them to suggest to their colleagues that they might wish to do likewise Surprisingly enough, many of the profession do not know of its existence or of its work. Many gladly subscribe when their attention is drawn to its purpose of acting as a Good Samaritan to the whole of the medical profession The Fund gives assistance to distressed members of the profession, their wives, widows and children Immediate help is given in urgent cases and all deserving applicants are treated impartially ”

Dr Anwyl-Davies appeals to subscribers, new and old “ to consider the very profitable and simple procedure of signing seven-year covenants ” Some 1275 already subscribe by covenant and last year £5845 was recovered, without further cost to the “ covenanted ” subscribers, from the Inland Revenue He also thanks those who remember the Fund in their wills—however small the legacy may be “ Last year the legacies received came to the welcome sum of £29,495, a very valuable addition to the accumulated funds ”

The report for 1956 mentioned that under the Giffen bequest a house was to be bought and equipped for indigent doctors A large closer alignment and explain why in some cases there is neither fibrosis nor thrombosis

Furthermore, support for some common factor may be found in Bedford and Konstam's[2] account of the postmortem findings in adult Africans dying of heart-failure of unknown ætiology Of 17 of these cases 3 had hypoplasia of the aorta, which is known to be associated with congenital fibroelastosis of the endocardium

Department of Pædiatrics,
Groote Schuur Hospital,
Cape Town

P M SMYTHE

INTRADERMAL TESTS FOR SERUM SENSITIVITY

SIR,—We are in full agreement with Dr Tasman and his associates[3] regarding the superiority of the intravenous route over the intramuscular in the antitoxin treatment of diphtheria, but we do think that it is an exaggeration of good therapy to advocate that route for all cases however mild and even for all suspected cases

We differ entirely from them, however, regarding the value of intradermal reactions of any kind as a means of detecting general sensitivity to serum They quote our article[4] of 1957, but do not mention a previous one[5] dealing with the subject generally and not only in connection with tetanus antitoxin administration We would refer them to that article

We both know of instances of severe allergic shock, some of them fatal, which have occurred following antitoxic serum given either intramuscularly or intravenously on the strength of a negative skin test On the other hand, one of us (L J M L) has had experience (in the course of titration of scarlatinal antitoxin on scarlet fever patients) of more than 50 cases, with strongly positive intradermal reactions to serum in a dilution of 1 in 10, but no general reactions whatsoever when given a full dose of scarlatinal antitoxin intramuscularly a few hours later Moreover, many of these patients still had positive skin tests when there could be no more question of general sensitivity remaining We have come to the conclusion—and many of our colleagues in various hospitals have, too—*that skin sensitivity and general sensitivity do not run parallel*

Since skin tests have proved so unreliable, we have used and recommended for years the method of a small trial dose of 0 2 ml of undiluted or diluted serum given subcutaneously for the purpose of detecting *general* sensitivity This method may, on rare occasions, cause allergic shock in hypersensitive patients, but owing to the small dose and the slow absorption this shock can be quickly controlled

Hither Green Hospital,
London, S E 13

L J M LAURENT

Wellcome Research Laboratories,
Beckenham, Kent.

H J PARISH

ANNUAL MEETING OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

SIR,—I am grateful to you for allowing me to use this opportunity of bringing to the notice of the profession that the College is holding its annual meeting this year on Sept 26 and 27 in Cardiff

As you know, the College has recently adopted the policy of holding meetings from time to time in provincial centres, and the first of these was held in Manchester in 1955 The purpose of the council in holding these meetings is to bring the College closer to its provincial Fellows and Members and to enable them to take part in some of its activities The council is particularly anxious that Members of the College shall join us at this meeting, and any other diplomates will of course be very welcome Fellows have already been notified individually

The meeting will consist of a reception at Cardiff Castle, kindly given by the Lord Mayor and Council of Cardiff, and a subscription dinner, both on Friday, Sept 26 Tickets for the dinner (two guineas each) and invitations for the reception can be obtained from the Secretary of the College, but the numbers for both events are limited and early application is necessary

On Saturday, Sept 27, the morning will be devoted to scientific exhibitions and surgical operations arranged by the local committee at the Cardiff Royal Infirmary, followed by a fork lunch, kindly given by the Board of Governors of the United Cardiff Hospitals

In the afternoon, at 2 30 P M, the statutory annual meeting of Fellows and Members will be held in the Reardon Smith Hall, and this will be followed by the conferment of the Honorary Fellowship of the College on Sir Russell Brain, Bt, who will afterwards deliver a lecture on The Cervical Spine

The council hopes that this meeting will prove to be as successful an event as was the meeting in Manchester, and we trust that our colleagues in Wales will make a special effort to attend

Royal College of Surgeons of England,
London, W C 2

J PATERSON ROSS

Obituary

JOHN BROCK BISHOP

M A, B M Oxon, T D

Dr J B Bishop, deputy superintendent of Broadmoor Institution, died at his home on Broadmoor Estate on Aug 4, at the age of 50

He was a scholar at the Merchant Taylors' School and later an exhibitioner at St John's College, Oxford, where he took his preclinical course, gaining second-class honours in physiology His clinical work was done at St Thomas's Hospital, London, and after qualifying in 1931 he served there as casualty officer and house-physician Later he was a clinical assistant at the West End Hospital for Nervous Disorders and house-physician at the Victoria Hospital for Children Until 1939 he was in private practice in Chelsea During the late war he served in the R A M C both at home and overseas in North Africa and Italy He was mentioned in despatches and received the Territorial Decoration with there bars After the war he continued to serve in a hospital ship He remained a keen member of the Territorials until his transfer to the Army Emergency Reserve He went to his last camp only a few weeks ago

In 1948 he joined the staff of Broadmoor, where he worked first as a medical officer and later as deputy superintendent From the outset he regarded this as his life's work Of these years V G S writes

" Brock Bishop's main interest professionally was not in the science but in the art of medicine and its social applications The organisation at Broadmoor gave him wide scope for his particular type of work, and his practical common sense was an invaluable asset in such an institution For two years he sustained practically the whole administration of the institution during the illness of the late Dr S G James, then medical superintendent

" For some years he was handicapped by a neurological condition which with his characteristic tenacity he forbade

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[2] Bedford D E, Konstam, G L S *Brit Heart J* 1946, 8, 236

[3] Tasman, A, Minkenhof, J E, Vink, H H, Brandwijk, A C, Smith, L *Lancet* 1958, i, 1299

[4] Parish, H J, Laurent, L J M, Moynihan, N H *Brit med J* 1957, i, 639

[5] Laurent, L J M, Parish, H J *ibid* 1952, i, 1294

The Lancet · Saturday 23 August 1958

GLANDULAR TOXOPLASMOSIS

A SURVEY OF 30 CASES

J K A Beverley
M D B Sc Sheff,
LECTURER IN BACTERIOLOGY
C P Beattie
M A, M B Edin, D P H
PROFESSOR OF BACTERIOLOGY
UNIVERSITY OF SHEFFIELD

IF the results of toxoplasma antibody surveys are to be believed—and there is at present no valid reason to doubt them (Cathie 1957, Feldman and Miller 1956)—subclinical toxoplasma infection is common in this country, as in others. A recent survey in Lincolnshire (Beattie 1957) showed that 36% of country-dwellers and 22% of town-dwellers had cytoplasm-modifying (dye test) antibodies (Sabin and Feldman 1948) to a titre of 1/16 or more.

By contrast, clinical manifestations of toxoplasma infection appear to be uncommon, but perhaps they are not so uncommon as is often thought.

In the two toxoplasma reference laboratories in London and Sheffield in 1950–56 congenital toxoplasmosis was diagnosed by serological and in some cases animal-inoculation methods in 110 cases, and probably many more went undiagnosed (Beattie 1957). Moreover it is estimated that from 20% to 35% of choroidoretinitis is due to toxoplasma infection, mostly congenital (Smith and Ashton 1955, Jacobs et al. 1956, Perkins and Beverley 1958).

Infection cannot all be congenital. Nor would one expect that the manifestations of acquired infection should always, as in the earlier reports, be severe. For these reasons Siim (1951) looked for evidence of toxoplasma infection in patients with fever of unknown origin. He found it, as did Gard and Magnusson (1951) and von Zeipel and Linder (1951), in patients with lymphadenopathy resembling "glandular fever." These results were confirmed in this country by Skipper, Beverley, and Beattie (1954), by Cathie (1954 a and b), and by Bateman (1957). In Denmark Siim (1956a) has encountered over a hundred such cases. He estimates that toxoplasmosis accounts for about 5% of cases of lymphadenopathy of unknown origin. In our experience it accounts for about 7% of cases clinically diagnosed as "glandular fever" but giving a negative Paul-Bunnell reaction.

The Present Series

The purpose of this paper is to direct attention to this glandular form of toxoplasmosis, which appears to be the commonest manifestation of acquired infection. Thirty cases are prescribed in summary form (table I), and the results of antibody studies on the relatives of some of the patients are shown (table II). Some of the cases have been reported already and others will be reported more fully elsewhere.

Discussion

It may well be asked how a diagnosis of toxoplasmosis can be made and on what basis the cases were selected for this report. Isolation of the parasite by animal inoculation is the most trustworthy method.

In cases 7, 11, 14, and 19 the diagnosis was confirmed by inoculation of ground-up gland material into mice. In cases 24, 25, and 29, this failed. Toxoplasms have been isolated by other workers from muscle taken by biopsy, from tonsils, from blood, and from saliva. We failed to isolate toxoplasms from the tonsils of patient 18, but the attempt was made 8 months after the start of her illness, and we also failed to isolate the parasites from the blood or saliva of patients 19 and 20. It should be noted that, as in the present instances, toxoplasms from man often prove of low virulence for, and fail to produce obvious illness in, laboratory animals, yet toxoplasma cysts may be found in their brains a month or more after inoculation.

Rarely is it possible to make the diagnosis by demonstrating the parasite in excised lymph-glands. Indeed this has only once been done with certainty, when Stanton and Pinkerton (1953) after long search found one cyst. This is the only form which can be definitely identified in tissue sections. Nor can the histological picture establish the diagnosis, though it may suggest it.

The morphological changes in lymph-nodes have been described by Stanton and Pinkerton (1953), Siim (1952), Lelong et al. (1954), and Bang (1957). From these accounts it might appear that there is little agreement as to the actual microscopical changes, but this is probably due more to lack of unanimity in nomenclature than to true histological differences. In most cases there is a reactive hyperplasia with scattered foci of histiocytic or epithelioid cells.

Robb-Smith kindly examined sections of glands from some of the patients in this series and reported that those from patients 10, 11, 15, 17, 19, 21, 22, 23, and 24 correspond with his description of "lymphohistiocytic medullary reticulosis" (Robb-Smith 1947). The glands from patients 7 and 25 were not so typical of this. He found a similar appearance in sections of lymph-glands submitted to him by Siim and Bang, who described the change (1957) as a focal medullary reticulosis. The reaction, although characteristic, is not specific. Robb-Smith has found it in kala-azar and in many cases of unexplained ætiology which until recently were not investigated serologically for evidence of toxoplasmosis. It is distinct from the appearances found in infectious mononucleosis with a positive Paul-Bunnell reaction. Recently sera from six patients have been sent to us for serological tests for toxoplasmosis because a histological diagnosis of lymphohistiocytic medullary reticulosis had previously been made. Two of them proved strongly positive (cases 10 and 15). A third was very suggestive (dye test 1/256 but negative complement-fixation test), while the remaining three gave only low titres.

As animal-inoculation methods are not always possible or successful, the diagnosis must often rest on serological tests. Those now in use are the complement-fixation test and the cytoplasm-modifying (dye) test. An important but difficult question is what titres should be taken to signify active infection.

One answer would be to accept titres above those found in the normal population. We have recently found (unpublished) that only 2 out of 1357 adult blood-donors had dye-test titres of 1/256 or more. That titre, in the presence of a clinical picture compatible with toxoplasmosis, might be accepted. Another answer would be to accept titres comparable to those found in persons from whom toxoplasms were isolated. In the present series that would mean dye-test titres of 1/1000 or more, and indeed in twenty-five of the cases here reported the titres are, or are nearly, of this order. On the other hand Jacobs et al. (1954) isolated toxoplasma from the eye of a patient whose dye-test titre before enucleation was 1/64, Prior et al. (1953) from the blood of a healthy young woman (owner of a toxoplasma-infected dog) whose dye-test titre was 1/160, and we ourselves (unpublished) from the ventricular fluid of a baby whose dye-test titre was 1/170 and whose complement-fixation titre was less than 1/5. Sabin et al. (1952) suggest that for proof of active infection the dye-test titre should increase eightfold or more to at least 1/256 and be maintained at or near that level for several weeks. During this time house in Putney is now to be converted into five self-contained flats each consisting of a bedroom, sitting-room, bathroom, and kitchen

During the year the Ladies' Guild distributed more than £13,000 This auxiliary helps with visiting, the education of children, the care of young widows, and the distribution of medical comforts, gifts of clothing, coal and other necessities Parcels of clothing, with the donor's name and address inside, should be sent to the clothes room, Ladies' Guild of the R M B F, Tavistock House (North), Tavistock Square, London, W C 1

At the annual general meeting on July 30 Sir Henry Tidy was re-elected president, Mr F A Juler hon treasurer, and Dr Anwyl Davies hon secretary The Fund's address is 1, Balliol House, Manor Fields, Putney, London, S W 15

THE BIRMINGHAM DENTAL HOSPITAL

The year 1958 is celebrated for many important centenaries in medicine, including that of this unique hospital—unique because it is the oldest dental institution in this country and possibly in the world

It was Samuel Adams Parker, a son of Langston Parker, the famous surgeon on the staff of the Queen's Hospital, who founded the Birmingham Dental Dispensary early in 1858 when he had but recently finished his dental studies at the Middlesex Hospital The first premises were at 13, Temple Street, and it is interesting that the committee set out to undertake not only extractions but also stoppings and scalings as well as "the regulation of children's teeth" C J Fox had in 1855 opened a similar dispensary in London, but it was not to last long The Birmingham Dental Dispensary, on the other hand, prospered and had already moved premises twice before the passing of the Dental Act in 1878 Its more active concern with teaching necessitated in 1882 a third move, this time to 71, New Hall Street When in 1900 Mason's College became the University of Birmingham, another move was soon required, and in 1905 the hospital occupied its present site which it has more than outgrown A fifth move, we hope, will not be delayed long

Mr R A Cohen has gone to great pains in preparing a history of the hospital[1] writing of the many devoted people who have served it so well in this hundred years

University of Oxford

On Aug 2 the following degrees were conferred

D M—G A Rose
B M—M A Pratelli

Shortage of Staff at York

Owing to shortage of junior staff in the surgical departments of York hospitals, admission to the surgical wards has been restricted (*Yorkshire Post*, July 30) At a meeting of the York "A" and Tadcaster Hospital Management Committee the secretary said there should be five house-surgeons at the city, county, and military hospitals, but in fact there was only one, which was not enough for proper supervision of the wards The consultant staff had therefore agreed for the time being to admit only emergency cases, urgent cases from the waiting-list, and some minor cases which would not need much supervision At the York Maternity Hospital, owing to a shortage of nurses, only one ward is being used

Future Role of the Special Hospitals

When he opened a £100,000 ward block at the Royal Orthopaedic Hospital, at Northfields, near Birmingham, on Aug 2, Sir Harry Platt said that there was a powerful school of thought whose adherents held that the day of special hospitals was over This was doubtless true of small special hospitals, situated in isolation and unable to share in the diagnostic facilities of the modern general hospital He was one who believed that a limited number of large special institutions would be needed for many years to come But such institutions must "justify their continued existence not only by providing for long-stay patients a comprehensive range of rehabilitation facilities, but must, under the guidance of the university medical schools, become centres of research and teaching"

Medical Research Council

The Council announce that they have made the following travelling awards for 1958–59

Rockefeller fellowship in medicine—Dr G Burnstock, research assistant, department of pharmacology, University of Oxford, Mr P J Holloway, external scientific staff member, M R C Laboratories, Hampstead, Mr W B Jennett, lecturer in neurosurgery, University of Manchester, Dr A P Mathias, lecturer in biochemistry, University College, London, Dr R P Michael, clinical research fellow, department of experimental neuroendocrinology, Institute of Psychiatry, Maudsley Hospital, London, Dr P H A Sneath, scientific staff member, National Institute for Medical Research, Mill Hill, London

Lederle fellowship in medicine—Dr R J Linden, lecturer in physiology, University of Leeds

Alexander Pigott Wernher fellowship in ophthalmology and otology—Dr G B Arden, research assistant, Institute of Ophthalmology, London

French exchange scholarships in medical science—Miss J E Cremer, scientific staff member, M R C, toxicology research unit, Carshalton, Surrey, Miss S Reiman, assistant lecturer in psychology, Institute of Psychiatry, Maudsley Hospital, London

The following awards have been made after nomination by the Council

Lilly fellowships in medicine—Mr J D Griffiths, senior registrar in surgery, St Bartholomew's Hospital, London, Dr C W M Wilson, lecturer in pharmacology and therapeutics, University of Liverpool

United States Public Health Service, National Institutes of Health, Bethesda, Maryland, fellowships in medical science—Dr B S Hartley, research fellow, department of biochemistry, University of Cambridge, Dr K W Cross, reader in physiology, St Mary's Hospital Medical School, London, Dr A Doig, medical registrar, Royal Infirmary, Edinburgh

Social Security Agreement with Yugoslavia

The convention on social security between the United Kingdom and Yugoslavia, which was signed on May 24, has now been ratified and will come into force on Sept 1 The convention covers cash benefits for unemployment, sickness, maternity, old age, widowhood, orphanhood, industrial accidents and diseases, death, and family allowances

Licence of Ravensburg Doctor Withdrawn

The Schleswig-Holstein Minister of the Interior has withdrawn the medical licence of Dr Herta Oberheuser At the annual representative meeting of the British Medical Association (see *Lancet*, July 19, 1958, p 148) a resolution was passed expressing distress that a doctor who had been convicted of medical war crimes should be allowed to return to medical practice

More Psychiatrists for Birmingham

On the recommendation of their consultant services committee Birmingham Regional Hospital Board have agreed to the appointment of 12 additional consultant psychiatrists in the region (*Birmingham Post*, July 24) Subject to the approval of the Ministry of Health, it is intended to fill 3 of the posts immediately The committee believe that it would be impossible to fill all 12 posts at once

Dr P H C Fowell has left the residue of his estate, almost £30,000, to the Imperial Cancer Research Fund

Surgeon Commander J Alexander, R N V R, has been awarded the Royal Naval and Royal Marine Forces Volunteer Reserve decoration

Surgeon Captain W P E McIntyre is to be promoted surgeon rear-admiral in November when he will succeed Surgeon Rear-Admiral R L G Proctor as deputy medical director-general of the Navy

Dr J T Hayward-Butt has been appointed assistant professor of anæsthesiology at the State University of Iowa

Dr M B McIlroy has been appointed an associate professor of medicine in the University of California

The Royal Society has awarded a Mr and Mrs John Jaffé donation studentship to Dr Jennifer Wildy to work on the biosynthesis of the protein and hæm components of hæmoglobin in the department of chemical pathology of University College Hospital Medical School really ill, and one (30) admitted to no more than having felt "off colour" The shortest duration was 1 week (patient 4) and the longest at least 44 weeks (patient 25) In general, adults and adolescents were more severely affected than children

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[1] The History of the Birmingham Dental Hospital and Dental School By R A COHEN L D S, F S A Published by the Board of Governors of the United Birmingham Hospitals

Among the first things noticed by twenty of the thirty patients, or by their parents, was swelling or pain in lymph-glands, usually in the neck In five cases (7, 11, 14, 16, 17) so little account was taken of this that 2–8 weeks passed before a doctor was consulted

Any group of neck glands may be affected Sometimes the enlargement was unilateral and sometimes bilateral In addition to glands in the neck, the axillary and inguinal glands were usually enlarged, and in three patients glands in the chest wall In one patient (8) X-ray examination revealed enlargement of hilar glands The size of the glands varied from 1 to 6 cm Some were soft, some rubbery, and some hard They were discrete and not attached to the skin In five patients (3, 8, 22, 24, 25) they were tender, patient 3 cried with pain, and the first symptom noted by patient 19 was glandular aching But in most cases tenderness, if present, was slight The glands as a rule took a long time, sometimes many months, to return to normal size

Sore throat was not a prominent symptom It was noted at the start in seven patients and developed later in three others Other first symptoms were headache, fatigue, depression, and muscle pain None of the patients had a high fever and eleven were afebrile The spleen was enlarged in five patients in two of whom the liver was also enlarged Siim (1956a) states that the spleen is seldom palpable

The patient whose initial symptom was headache (24) had also pain in the back and neck which led to a suspicion of poliomyelitis Three others developed headache during their illness (20, 25, 26), and patient 26 was suspected of having meningismus Here, perhaps, may be seen a transitional stage towards the rare severe cases of toxoplasmic encephalitis

Pain in the joints and limbs was experienced by three patients (19, 24, and 25) and has been observed by Stanton and Pinkerton (1953) and by Garin (1953)

Abdominal pain was present in three (19, 23, 25), from one of whom (19) an apparently normal appendix was removed It seems possible that toxoplasmosis may cause mesenteric adenitis

TABLE I—*continued*

Case no	Sex and age	Date of onset	Fever	Sore throat	Enlarged spleen	Enlarged glands and other points of interest	Illness (weeks)	Leucocytes	Lymphocytes	Date	Dye test	C F T	Animal contact
18	F 16	iv 56	Sl	Yes		Tonsillar and cervical Little constitutional upset		9200		26 vi 56	1/960	1/80	Farm animals
19*	F 17	14.xi 56	Yes	Yes	No	Submental, anterior border of sternomastoid, posterior triangle of neck, groin All on right. Ached at first. Later tender Discrete except at the anterior border of sternomastoid Overlying skin not involved Shoulder, leg, and abdominal pain Appendicectomy Tired	22	8000	2900	24 x 56 30 x 56 14.xi 56 21.xi 56 26.xii 56 9 i.57 16 ii.57 10 v.57 4 xi.57 31 iii.58	1/44,000 1/50,000 1/32,000 1/17,000 1/9000 1/8200 1/7000 1/1100 1/320 1/340	1/10 1/20 1/40 1/20 1/5 1/5 1/10 <1/5 <1/5 <1/5	Dogs and hens
20	F 19	24 xii 54	Sl	Sl	No	Neck, axillæ, skull, headache, nausea, depression, fatigue	28	7200	3200	8.ii.55 8 iii 55 5 vii.55	1/226 1/900 1/500	1/8 1/32 1/14	Cats and farm animals
21	M 19	1.ii.56	No	No	No	Neck. Swelling of upper gum, small ulcers in lower lip No general upset	8	8000	2500	14 iii 56 7 v.56	1/1000 1/6000	1/5 1/40	Much with dogs
22	F 21	20 vi.56	No	No	No	Neck. Firm, slightly tender Tired, irritable, ambulant	4	6000		10 viii 56 14.ix.56	1/400 1/3000	1/2 1/10	Cats
23†	M 21	6.x.54	Yes	Yes	Yes	Right side of neck, axillæ, groins, rubbery, not tender Sore throat, abdominal discomfort, tachycardia	24	9600	2600	9.ii.55 17.iii.55 17.ii.56	1/256 1/3200 1/400	1/64 1/32 <1/5	Dogs
24†	F 26	10 viii.56	Sl. 1 day	Slight after second admission	No	Left occipital, right cervical, right axillary, right inguinal, supraclavicular, discrete, firm, tender First admitted for headache and back pain Glands enlarged after discharge Readmitted	16	8200	3450	17 viii.56 23 viii.56 22 xi.56 13 xii.56 13.xii.57	1/77 1/102 1/4600 1/12,000 1/850	 1/5 1/20 1/20 <1/5	Dogs and farm animals
25	M 27	14.iii.56	Sl.	Sl.	No	Cervical, axillary, inguinal Tender in left groin Severe lumbar pain, also pain in axilla, chest, back, groin and abdomen, slight cough, stiffness of right wrist and hand. Relapse in Jan, 1957 Prolonged fatigue	44	10,800	4300	26 iv.56 16 v.56 31 v 56 8.xi 56 2.ii.57	1/1000 1/1000 1/730 1/175 1/270	1/5 1/10 1/5 <1/5 <1/5	Horses and dogs
26	M 30	3.xi.55	Yes	Yes	No	Cervical and postauricular Severe headache. Prolonged fatigue	40	10,000	5000	11 viii 55 17.xi 55 23.ii.56	1/2000 1/10 200 1/7800	1/64 1/40 1/80	Dogs
27	F 32	i 57	Yes	Yes		Left posterior cervical		9600		4.iv 57	1/400	1/10	Budgerigar
28	F 36	31.xii.56		Yes	No	Neck, hard and shotty Preceded by sore throat	10	7700	3500	28.xii 56	1/1100	<1/5	
29	F 50	ii.54	No	No	No	Neck. Weakness and shortness of breath	26	10,000	7000	22.iv 54 30 iv.54	1/1170 1/5100	 1/16	None
30	F 50	i.55	No	No	No	Axillary, not noticed by patient. 'Off colour' Mother of patient 19				18 ii 55 22.iii.55	1/820 1/560	1/16 1/64	Cats and farm animals

* Toxoplasma recovered from gland by mouse inoculation † Reported in greater detail by Beverley et al (1958) ‡ Reported in greater detail by Paton et al (1958)
C.F T = complement-fixation test Sl. = slight.

the level of the complement-fixing antibody should either change from negative to positive and rise to a titre of 1/8, or, if positive initially, should subsequently increase at least fourfold A rise in titre is of great value, but repeat specimens cannot always be obtained Moreover the antibody titre may be at its highest when the first specimen is taken

For this report we have adopted an arbitrary level of a dye-test titre of 1/256 and a complement-fixation titre of 1/10 *This does not prove toxoplasmosis but makes it* very highly probable We have departed from this in only two cases—in case 2 because the rise in dye-test titre seems to justify inclusion and in case 4 because the dye-test titre was 1/875 though the complement-fixation titre was only 1/4 The titres chosen have meant the regretted omission of numerous other cases believed to be toxoplasmosis, some of which will be mentioned later

It should be noted that titres may not reach the arbitrary level till some time after the onset of symptoms After laboratory accidents, when the development of toxoplasmosis was expected and the onset of symptoms looked for, the interval has been 1–4 weeks

It was hoped that a study of the case-records would show characteristic features which would enable glandular toxoplasmosis to be diagnosed clinically, but it has not done so The diagnoses considered by the attending physicians were varied Most common was infectious mononucleosis Others were tonsillitis, Hodgkin's disease, mumps, lymphosarcoma, leukæmia, aleukæmic leukæmia, and poliomyelitis

In their nature and variety the signs and symptoms resemble these of infectious mononucleosis Only one thing stands out None of the patients' sera gave a positive Paul-Bunnell reaction This has also been the experience of Siim (1956a)

As with infectious mononucleosis, the incidence is mainly in children and young adults Ten of the patients were under the age of 10, *eleven from 11 to 20, four from* 20 to 30, and five over 30 This predominance in the young is in keeping with the results of serological surveys (Beverley et al 1954) which show that in this country the frequency of toxoplasma antibodies rises to the age of 20 and thereafter changes little

The illness varied enormously in severity and duration Five of the patients (7, 10, 12, 13, and 17) were never

TABLE I—SUMMARY OF THE CASES

Case no	Sex and age	Date of onset	Fever	Sore throat	Enlarged spleen	Enlarged glands and other points of interest	Illness (weeks)	Leucocytes	Lymphocytes	Date	Dye test	C.F.T	Animal contact
1	M 3	10 xii 56	Yes	No	No	Tonsillar, neck, axillæ, groins, not tender Photophobia	3	11,500	5200	21 xii 56 22 i 57	1/900 1/900	1/10 1/40	Cats, dogs, rats, budgerigar
2	M 3	xi.56		Sl	No	6 months' recurrent, enlargement of parotids Tonsillitis Recovered, then relapse of neck swellings		15,000		12 iv 57 19 vii 57	1/14 1/320	<1/5 <1/5	
3	M 5	25 xi 56	Yes	Yes	Yes also liver	Neck, supraclavicular, axillary, inguinal, neck painful Also tonsillitis	4	19,500	11,500	13 xii 56 21 xii 56 23 i 57 20 iii 57	1/200 1/160 1/500 1/55	<1/5 1/10 1/5 <1/5	Cats, dog, rats, mice, budgerigar
4	M 5	11 xi 55		Yes		Neck Sore throat, vomiting	1	6800		25 xi 55	1/875	1/4	
5	M 6	14.xii.56	Sl.	Yes	No	Neck, axillæ, groins, preceded by sore throat	3	8000	4080	1 ii 57 12 iv 57	1/340 1/1000	1/10 1/40	None at home
6	F 6	24 i 53	Sl			Neck and groin Preceded by "influenza" and bronchial catarrh	7	12,500	4500	18 ii 53 13 iii 53	1/360 1/150	1/16 1/8	
7*	M 7	18 x.55	No	No	Yes	Neck, axilla, groins Did not feel ill 5 weeks before doctor consulted	8	6800	3260	9 xi 55 1 iii 56	1/560 1/1200	1/5 1/20	Cats
8	M 8	20 vi 55		No	No	Anterior and posterior triangles of neck, and hilar Tired	8	8900	3000	23 vii 55 11 viii 55 24 xi.55	1/125 1/1250 1/1800	1/16 1/24 1/40	None at home
9	M 8	8 i.57	Yes		Yes	Neck, especially submandibular, soft and discrete Preceded by malaise and fever	4	16,000	8800	2 ii 57 19 ii 57 18 iv 57	1/320 1/340 1/85	<1/5 1/10 1/20	Cat
10	F 9	x.57	No	No	No	Neck, axillæ, groins, chest wall Not tender Size from pea to egg Did not feel ill		5000	Normal	15 i 58	1/3200	1/80	
11*	M 11	11 i 55	Yes			Axilla, chest Fever at start. 4 weeks *before doctor consulted*	8	6300	3100	18 iii 55	1/1600	1/8	Domestic and farm
12‡	M 11	11 iii.55	No	No	No	Right axilla and below right breast. Rubbery Not tender Did not appear ill	3	9700		25 iii 55 28 iv 55 12 i 56	1/820 1/256 1/38	1/8 1/16 <1/5	Dog
13	M 14	x 56	No	No	No	Occipital only Did not feel ill		7200	No l'cytosis	4 v 57	1/4800	1/80	Mice
14*	F 14	1.xi.57		No	Yes	Post- and pre-auricular, occipital, shotty 4 weeks before doctor consulted	2	7200	4320	13 ii 57 20 xii 57 23 iv 58	1/17,000 1/32,000 1/2800	1/40 1/20 1/80	Budgerigar sick May to Sept., also dog and cat
15	F 14	ix.56	No	No	No	Occipital and cervical, smooth, painless, freely movable Throat infection 3 months before		5500	2250	1 vi.57	1/10,000	1/80	Pet bird
16	M 15	ii 57	No	No	No	Occipital, axillæ and groins, firm and discrete 2 months before doctor consulted		6850	2945	5 vii 57 7 ix 57	1/7000 1/4000	1/40 1/20	Dog ill with "twitchings" Jan 1957
17	M 16	18.x.54	No	No	No	Neck, axilla 2 weeks before doctor consulted Never really ill		7200	3310	11 i 55 5 iii.55	1/3000 1/3500	1/80 1/32	Cat

of subclinical infection years before Relatives of patients 2, 5, 12, and 20 appear, however, to have been infected about the same time as the patient On retrospective examination glandular enlargement was found in the mother of patient 20 and a brother of patient 12 In the other instances there was no history of recent illness nor were there enlarged glands It is already obvious, from antibody surveys, that sub-clinical infection must be much more common than clinical

Infection in these instances might have been from a common source, might have been from the patient, or might have been from one of his subclinically infected relatives There is as yet no definite evidence of man-to-man transmission Cathie (1954b), however, not only suggested this, but also a possible means of transmission, when he isolated the parasite from the saliva of a child Jacobsson (1953) reported that a father developed a febrile illness a fortnight after the onset of lymphadenopathy in his son Several of Siim's (1951) cases were in members of the same family or in playmates In the present series patient 12 and his 8-year-old brother slept in the same bed Against the theory of human transmission it must, however, be stated that the incidence of positive serological reactions in husbands and wives is no different from what would be determined by the laws of chance

Until more is known it must be assumed that human infection may come from a variety of birds and mammals, including man Toxoplasma has been found in the urine, fæces, and saliva of animals and in the saliva of man Infection might be by direct contamination, by contamination of food, or by consumption of uncooked meat It is very unlikely that consumption of cooked meat could produce infection or even give rise to the production of antibodies, for Rawal (1957) found no difference in the incidence of toxoplasma antibodies in vegetarian Hindus and in meat-eating Christians and Moslems Transmission by an insect vector cannot be ruled out, but many attempts to prove it have failed

TABLE II—ANTIBODY TESTS ON MEMBERS OF PATIENTS' FAMILIES

—	Dye test	Complement-fixation test
Patient 1	1/900	1/40
Father	1/46	<1/5
Mother	1/100	1/5
8 other relatives in close contact—all negative except for one with dye-test titre of 1/46		
Patient 2	1/500	1/5
Father	1/80	<1/5
Mother	1/76	<1/5
Brother, 13 yrs	1/24	<1/5
Sister, 7 yrs	1/880	1/5
Brother, 3 yrs	1/1600	1/10
Brother, 2 yrs	1/5000	1/40
Patient 5	1/1000	1/40
Mother	<1/4	<1/5
Brother, 7 yrs	1/320	1/40
Patient 9	1/340	1/10
Father	1/94	<1/5
Mother	1/80	1/5
2 sisters	<1/8	<1/5
Patient 12	1/820	1/8
Brother 8 yrs (tested 10 months after illness of patient 12)	1/200	1/5
8 other members of household	<1/16	<1/5
Patient 13	1/4800	1/80
Mother	1/160	<1/5
Father and 2 sisters	<1/4	<1/5
Patient 16	1/4000	1/20
Mother	1/8	A C.
Sister	1/5	<1/5
Patient 18	1/50,000	1/20
Father	1/92	<1/5
Mother	<1/4	<1/5
Patient 20	1/900	1/32
Father	1/56	<1/5
Mother (case 29)	1/820	1/16
Brother	1/4	<1/5
Patient 23	1/3200	1/32
Mother	1/40	1/10
Father, 2 brothers, and 1 sister	<1/32	<1/5
Patient 25	1/1000	1/10
Wife	1/15	<1/5
3 children, 1 born while patient was ill	<1/4	<1/5
Patient 26	1/10,200	1/40
Wife	1/47	<1/5
Baby born while patient was ill	1/76	<1/5 (passive transfer)

A C. = anticomplementary

Lymphadenopathy appears to be the commonest manifestation of acquired toxoplasmosis There may be other minor manifestations—perhaps some of the febrile episodes so common in childhood

This is suggested by the finding of high-titre antibodies (dye test 1/1000, complement-fixation test 1/40) in a boy of 2 years (Radcliffe Infirmary no 219832) who developed a few days of fever after a fall He had no glandular enlargement His brother, aged 5, tested nine months later had a dye-test titre of 1/130 and a complement-fixation titre of 1/5 He had not been ill Significant titres were not obtained on serum from the father and mother

Since the commonest manifestation of acquired toxoplasmosis so far recognised is lymphadenopathy which usually begins in the neck, it is tempting to think that infection takes place through the mucous membrane of the tonsillo-pharyngeal region

Summary

Thirty cases of acquired toxoplasmosis resembling glandular fever are reported Four were proved by the isolation of the parasite The others had dye-test antibody titres of from 1/320 to 1/50,000 and complement-fixing titres from >1/5 to 1/80 All had negative Paul-Bunnell reactions

Ten of the patients were under the age of 10, eleven from 11 to 20, four from 20 to 30, and five over 30

Lymphocytosis was found in fifteen and cells of "glandular fever" type were reported in five Sore throat was present in ten

The severity and duration of illness varied enormously Five of the patients were never really ill, whereas in others the illness dragged on for months In such cases fatigue was prominent. None had a high fever and eleven were afebrile

Diagnosis and sources and modes of infection are discussed

We gratefully acknowledge the help given to us by the many physicians and pathologists who supplied us with material from, and information about, the patients We also thank Dr A H T Robb-Smith and Dr R Curran for examining sections and Miss Geraldine Calton, A I M L T, for her skilled technical assistance

Case 21 is published by kind permission of the Director of Medical Services, Royal Air Force

The work was assisted by a grant from the Medical Research Council

REFERENCES

Alexander, C M Callister J W (1955) *Arch Path* 60 563
Bang F (1957) *Bull Cancer*, 44 60
Bateman M (1957) *Brit med J* ii 141
Beattie, C. P (1957) *Trans R Soc trop Med Hyg* 51, 96
Beverley, J K A., Beattie, C P Roseman C (1954) *J Hyg Camb* 52, 37
— Fry, B A (1957) *Brit J Pharmacol* (in the press)
— Skipper, E, Marshall, S C (1955) *Brit med J* i, 577
— Caley J P Warrack, A J N (1958) *J clin Path* 11, 119
Cathie, I A B (1954a) *Lancet*, i, 813
— (1954b) *ibid* ii, 115
— (1957) *Trans R Soc. trop Med Hyg* 51, 104
Couvreur, J (1955) Thesis Paris
Desmonts G (1958) Personal communication
Eyles D E (1956) *Ann N Y Acad Sci* 64, 252
Farquhar, H C (1950) *Lancet*, ii, 562
Feldman H A, Miller, L T (1956) *Amer J Hyg* 64, 320
Finckh E S (1954) *Med J Aust* 41, 965
Gard S, Magnusson H. J (1951) *Acta med scand* 141, 59
Garin J P (1953) Thesis, Lyon
Jacobs L. Fair J R., Bickerton, J H (1954) *Arch Ophthal* 52, 63
— Melton, M L, Cook, K (1955) *J Parasit* 41, 353
— Naquin H, Hoover, R, Woods, A C. (1956) *Bull Johns Hopk Hosp* 99, 1

references continued overleaf

One patient, not included in this list because, although her dye-test titre was 1/280, her complement-fixation titre was >1/5, had enlarged mesenteric glands 7 months before the enlargement of glands in neck Another had for 2½ years recurrent attacks of pain in the right iliac fossa diagnosed as recurrent mesenteric adenitis or subacute appendicitis A normal appendix was removed but the mesenteric glands were found to be enlarged A month before operation his dye-test titre was 1/540 and his complement-fixation titre 1/80 4 months after operation the results were 1/900 and 1/20 He too has been excluded from the list because confirmation by isolation of the parasite is thought necessary before accepting toxoplasmosis as a cause of mesenteric adenitis unassociated with lymphadenopathy elsewhere

Joseph et al (1957) isolated toxoplasma from an axillary gland of a patient who had mesenteric adenitis, but failed to isolate it from the mesenteric glands of twenty-two others, two of whom had serological reactions indicating recent toxoplasma infection More recently Desmonts (1958) examined the serum of a child who was operated on for appendicitis and found to have mesenteric adenitis The results on a specimen taken 5 days after operation were dye test, 1/100, complement-fixation test, negative 3 weeks later the titres had risen to dye test, 1/2500, complement-fixation test 1/100

Reid and Manning (1956) noted symptoms attributable to mesenteric adenitis in three of their thirteen patients, and in both of Pinkerton and Henderson's (1941) fatal cases of typhus-like toxoplasmosis the mesenteric glands were enlarged Makstenieks and Verlinde (1957) isolated toxoplasms from the mesenteric glands of inoculated monkeys

Fatigue was common and in some cases long-continued Possibly this may be due to infection of the musculature, for toxoplasms have been demonstrated in, or isolated from, muscle tissue (Kass et al 1952, Couvreur 1955, Siim 1956b, Kayhoe et al 1957)

The blood-picture showed an absolute leucocytosis in six patients, while five others, adults, had leucocyte-counts of between 9000 and 10,000 per c mm Lymphocytosis (under 5 years, >6000, over 5 years >3000) was found in fifteen patients In most it was slight and the highest figure recorded was 11,500 per c mm Cells of "glandular fever" type were reported in six patients (4, 14, 19, 22, 27, and 28) while atypical cells not typical of glandular fever were reported in patient 21 A high eosinophilia, 3150 per c mm, was found in only one patient (2) Patients 1, 5, 6, and 25 had eosinophil-counts of from 400 to 700 Of these patients no 1 suffered from asthma and infantile eczema From only one of the patients (19) was bone-marrow taken for examination The hæmatological report on this was that it was normal apart from apparent "glandular fever" cells, but of considerable interest was the discovery of bodies morphologically resembling toxoplasma Unfortunately no bone-marrow was left for mouse inoculation and, as the patient had experienced considerable pain, it was not thought justifiable to repeat the marrow puncture This is to be reported in greater detail elsewhere

In none of the patients was a rash reported, but patient 25, 2 days after he took ill, had a red elevated irregular area on the skin of the outer surface of his left leg In two other probable cases (not included) a rash was found

One was of a boy aged 12 who, besides glandular enlargement, had a discrete, papular, erythematous rash, at first over the body and later confined to the trunk His dye-test titre was 1/190 and his complement-fixation titre 1/16 The other was of a man aged 21 who had a sparse macular rash on the trunk His axillary, inguinal, and posterior cervical glands were enlarged, he had a lymphocytosis, and atypical mononuclear cells were found in his blood His dye-test titre was 1/160 and his complement-fixation titre 1/10 The Paul-Bunnell reaction was negative in both cases

Only one of the patients (25) had pulmonary symptoms They were slight cough and sharp pain in the left lower chest, accentuated by deep breathing In another (8) enlarged hilar glands were found on X-ray examination

No serious sequelæ were observed in the present series, but Wising (1952) and Kayhoe et al (1957) reported choroidoretinitis, and one of Strom's (1951) patients developed myocarditis, meningeal irritation, and encephalitis The second patient of Kayhoe et al had increased protein and cells in the cerebrospinal fluid There is also a possibility, suggested by Finckh (1954) and by Siim (1956a), that malignant changes may take place in the glands

A particular danger is the development of toxoplasmosis during pregnancy, because the infection may be passed to the fœtus As a rule the mother's infection passes unnoticed, but Couvreur (1955) on careful inquiry found evidence of illness in seventeen of twenty mothers In seven it was asthenia and in six lymphadenopathy Farquhar (1950) also noted lymphadenopathy in a woman who gave birth to a child with congenital toxoplasmosis, and Alexander and Callister (1955) and Siim (1956b) have found toxoplasms in both mother and child

The remedy found most effective, so far, in trials on animals is a combination of sulphadimidine and pyrimethamine (Eyles 1956, Beverley and Fry 1957) Jacobs et al (1956) and Perkins et al (1956) found this of some value in toxoplasmic uveitis, and Wettingfield et al (1956) and Kayhoe et al (1957) in toxoplasmosis with glandular enlargement Only one patient in this series (19) was treated with this combination During treatment her temperature fell but her illness persisted

An important question, to which there is as yet no satisfactory answer, concerns the source of human toxoplasmosis Animals have often been suspected and toxoplasmosis has been found in patients closely associated with infected dogs, cats, and rabbits In the present series patient 21 had much contact with 7 guard dogs, 3 of which had dye-test titres of over 1/160 No illness, however, had been noted in the dogs nor did their handlers have high titres Patient 23 was a veterinary student and exposed to particular risk because he had examined toxoplasma-infected dogs post mortem Patient 25 was a carter and had previously kept greyhounds No toxoplasma antibodies were found in the blood of his horse nor in others that he handled Twelve of the patients had contact, in some cases close, with cats

Cats associated with patient 1 had dye-test titres of 1/400 and 1/70, with patient 3 of 1/70, 1/9, 1/5, 1/25, and 1/160, with patient 17 of 1/128, and with patient 23 of 1/85 and 1/95 Toxoplasms were isolated from brain of the cat with a dye-test titre of 1/160 It was not attempted in the cats with dye-test titres of less than 1/50 and failed in the others Jones et al (1957) isolated toxoplasms from 50% of cats with titres of 1/64 or higher

Five of the patients had contact with budgerigars

Patient 14 had as her personal pet a bird which had been sick with vomiting on several occasions from May to September The husband of patient 27 bred budgerigars The birds in contact with patients 1 and 3 did not, however, have detectable antibodies to toxoplasma

In several instances members of a patient's family were also examined for antibodies This yielded interesting results, which are shown in table II In the case of patients 1, 9, 13, 16, 19, 23, 25, and 26 the relatives had either no antibodies or low-titre antibodies believed to be the legacy

TABLE II—EFFECT OF THYROXINE ON MEAN REACTION TIMES OF MYXŒDEMATOUS PATIENTS

Age	Mean reaction time (sec)			
	No of persons	Before therapy	After therapy	Normal mean
<40	4	0 303	0 2287	0 2286
40–50	7	0 322	0 2374	0 2396
50–60	7	0 317	0 2466	0 2546
>60	6	0 423	0 2570	0 2598

These normal ranges are also shown in table I There was no statistically significant difference between repeated readings in healthy people on different dates The reaction times of the 10 severely anæmic patients all fell within these normal ranges The mean values for the reaction times of the 50 hypothyroid patients for each age-group are also shown in table I There is a significant difference between each and the corresponding normal mean It can be seen from fig 2 that the reaction times of 46 of these patients lay outside the normal ranges The reaction times of the 9 myxœdematous patients who had been euthyroid for a considerable period were all within the normal ranges for their ages During therapy the reaction times of the myxœdematous patients decreased, and it can be seen (fig 3) that, when 23 of the 25 patients had become euthyroid, their reaction times lay within the normal ranges This happened both in the patients observed at intervals and in those in whom the test was repeated only when they were euthyroid These changes are statistically significant One patient, while hypothyroid, had a reaction time just within the normal range, but after treatment her "normal" reaction time was faster than normal for her age In a cretin, aged 14, who had neglected to continue her treatment there was also an improvement on further therapy, but, when she was euthyroid, her reaction time was still much prolonged This improvement corresponded to a clinical impression of increased alertness, although she still remained mentally retarded Table II shows the mean reaction times (excluding this case) before and after therapy For each age-group the values when the patients had become euthyroid, approached the mean for healthy people The improvement in the reaction times in the hypothyroid patients after treatment paralleled the changes in B M R

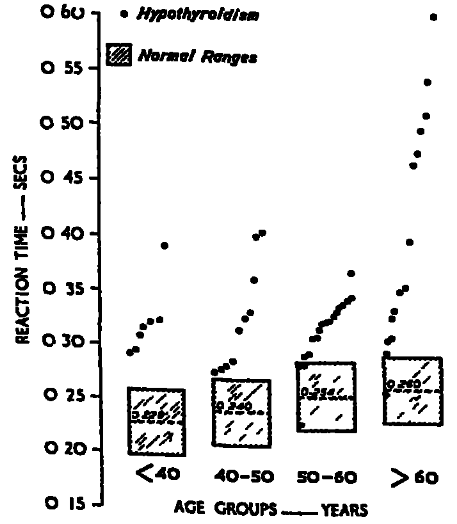

Fig 2—Reaction times of 50 hypothyroid patients showing the prolongation outside normal ranges (hatched areas)

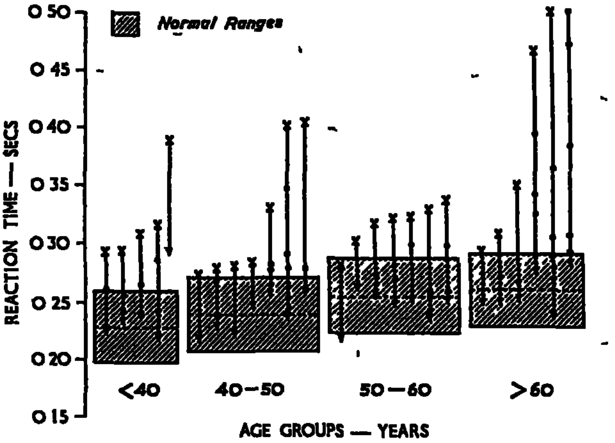

Fig 3—Effect of therapy on reaction times of 25 hypothyroid patients x, initial reading, ●, readings during period of control, v, final reaction time when patient was euthyroid

and serum-cholesterol levels This pattern is illustrated by fig 4, which shows the response to triiodothyronine in a myxœdematous female aged 44 The reaction time improved rapidly and within four days was within the normal range, where it has remained for a year

In both the healthy people and the myxœdematous patients dexamphetamine sulphate decreased the reaction time However, as can be seen in fig 5, this decrease was greater and more prolonged in the myxœdematous patients than in the healthy people The mean maximal quickening for the patients was 0 0524 seconds, compared with 0 0248 seconds for healthy people

Discussion

The method of measuring reaction time used in this study has many advantages over other methods In particular the apparatus is portable and inexpensive and allows considerable accuracy in timing The rapidity with which observations may be repeated also permits allowance

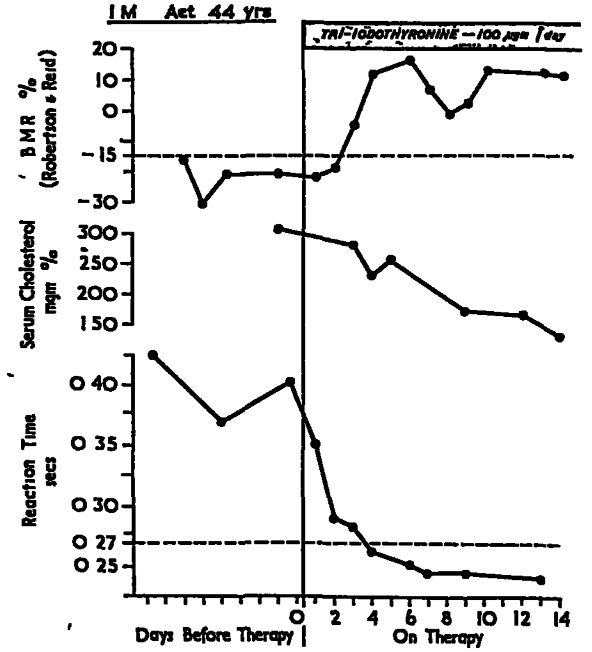

Fig 4—Effect of triiodothyronine on B M R., serum-cholesterol level, and reaction time in a myxœdematous patient

THE REACTION TIME IN MYXŒDEMA

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The reaction time, which measures the interval between the application of a stimulus to a sensory organ and a voluntary response, is known to be influenced by various factors Increasing age and fatigue, for example, lengthen it, as do depressant drugs such as alcohol and the barbiturates It seemed possible that the reaction time would also be prolonged in myxœdema, and that it might be correlated with the degree of thyroid underactivity A simple and rapid method of measuring the reaction time to a visual stimulus was therefore devised and has been used in healthy people, anæmic patients, and patients with myxœdema The effects of specific therapy and of dexamphetamine sulphate on the reaction time have also been studied

Method

The circuit of the apparatus used to measure reaction time is shown in fig 1 After the subject has depressed key 2, the observer depresses key 1, thus closing the relay contacts AB and CD As a result the red lamp lights, and the scaling unit is operated by the relay contacts AB and key 2 acting via the electronic gate The scaling unit records pulses at twice the mains frequency (100 c p s) until key 2 is released by the subject, when the scaler stops (again using the electronic gate) and records the reaction time in seconds up to 9 99 secs

The subject is instructed to depress the button (key 2) and, immediately he sees the red light, to remove his finger from the button as rapidly as possible The operator continues to keep his key depressed until after the scaler has stopped and then resets the scaler Several practice tests were made with each subject to ensure that the instructions were understood Reaction times were measured at irregular intervals of 5–10 seconds to avoid anticipation Long intervals were avoided to prevent the subject's attention from wandering In 5 healthy people and 4 myxœdematous patients a minimum of two hundred consecutive readings were taken After the first ten to fifteen tests had been made, there was little difference between the mean of each succeeding group of ten Accordingly, for each person fifty readings were taken, the first twenty being discarded, and the mean of the last thirty recorded as the reaction time A visual stimulus was used rather than aural because myxœdematous patients often have impaired hearing

TABLE I—MEAN REACTION TIMES

Age (yr)	Healthy			Hypothyroid	
	No of persons	Mean (sec)	Normal range M ± 2S	No of persons	Mean
<40	34	0 2286	0 1974–0 2598	7	0 3200
40–50	21	0 2396	0 2084–0 2708	10	0 3053
50–60	26	0 2546	0 2234–0 2858	18	0 3141
>60	20	0 2598	0 2286–0 2910	15	0 4313
Total	101			50	

Control subjects —This group consisted of 101 healthy people aged 17–83 years and included medical staff, laboratory personnel, and patients in whom there was no evidence of thyroid dysfunction A further 10 persons with normal thyroid function but with anæmia from various causes (hæmoglobin less than 60%) were also studied In 5 healthy people the test was repeated at intervals of several weeks

Hypothyroid patients —50 patients were studied The condition was idiopathic in most cases but in some it was secondary to hypopituitarism, Hashimoto's thyroiditis, thyroidectomy, or radio-iodine therapy Radio-iodine studies and estimations of basal metabolic rate (B M R) and of serum-cholesterol level were made in most subjects If the diagnosis was uncertain on clinical grounds, a final diagnosis was made only after the results of the administration of *l*-thyroxine sodium were known 20 of the patients were reviewed at intervals during therapy, and repeated estimations of B M R , serum-cholesterol level, and reaction time were made In 5 patients the reaction times were determined only before and after return to the euthyroid state to eliminate the possible effects of practice Reaction times were also estimated in a further 9 patients with proved myxœdema who had been euthyroid on thyroxine therapy for periods of six months to two years In all cases it was ascertained that no barbiturate was being administered

Dexamphetamine sulphate —This drug was administered orally in a dosage of 15 mg to 6 healthy people and 7 myxœdematous patients, and the reaction time was recorded at intervals for the following four to four and a half hours

Results

The mean reaction times of the healthy people for the four age-groups analysed are shown in table I The pooled standard deviation is ±0 0156 seconds If M is the mean of a group and S the pooled standard deviation, then, if the members are normally distributed, the range M±2S is one in which 95% of the normal reaction times will lie

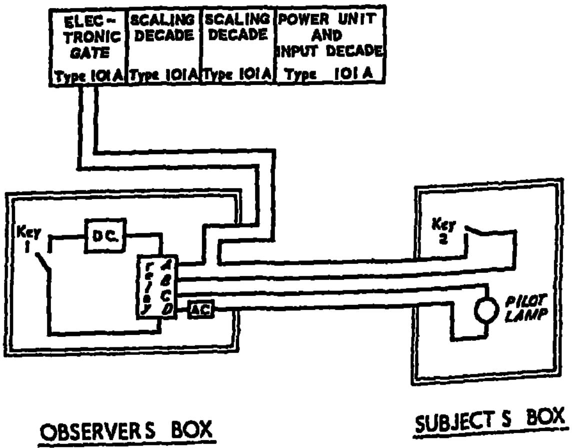

Fig 1—Circuit diagram for apparatus used to measure reaction time

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DR BEVERLEY REFERENCES—*continued*

Jacobsson, E (1953) *Nord Med* 49, 815 (Abstr *Trop Dis Bull* 1953, 50, 855)
Jones, F E , Eyles, D E , Gibson, C L (1957) *Amer J trop Med Hyg* 6, 820
Joseph, R , Desmonts, G , Job, J -C , Couvreur, J (1957) *Arch franc Pédiat* 14, 405
Kass, E H , Andrus, S B , Adams, R D , Turner, F C , Feldman, H A (1952) *Arch intern Med* 89, 759
Kayhoe, D E , Jacobs, L , Beye, H K , McCullough, N B (1957) *New Engl J Med* 257, 1247
Lelong, M G , Desmonts, L T , Vinh, L T , Nézelof, C , Satgé, P , Couvreur, J (1954) *Arch franc Pédiat* 11, 1092
Makstenieks, O , Verlinde, J D (1957) *Doc Med geog trop* 9, 213
Paton, J P J , Dick, A , Beverley, J K A (1958) *Scot med J* 3, 249
Perkins, E S , Smith, C H , Schofield, P B (1956) *Brit J Ophthal* 40, 577
— Beverley, J K A (1958) *Trans ophthal Soc U K* (in the press)
Pinkerton, H , Henderson, R G (1941) *J Amer med Ass* 116, 807
Prior, J A , Cole, C R , Docton F L , Saslaw, S , Chamberlain, D M (1953) *Arch intern Med* 92, 314
Rawal, B D (1957) Personal communication
Reid, J D , Manning, J D (1956) *N Z med J* 55, 448
Robb-Smith, A H T (1947) in Recent Advances in Clinical Pathology (edited by S C Dyke), p 350 London
Sabin, A B , Feldman, H A (1948) *Science*, 108, 660
— Eichenwald, H , Feldman, H A , Jacobs, L (1952) *J Amer med Ass* 150, 1063
Siim, J C (1951) *ibid* 147, 1641
— (1952) *Acta path microbiol scand* 30, 104
— (1956a) *Ann N Y Acad Sci* 64, 185
— (1956b) *VIII Int Congr Pædiat* Conference on Clinical Aspects and *Diagnostic Problems of Toxoplasmosis in Pædiatrics*
Skipper, E , Beverley, J K A , Beattie, C P (1954) *Lancet*, i, 287
Smith, C A , Ashton, N (1955) *Brit J Ophthal* 39, 545
Stanton M F , Pinkerton, H (1953) *Amer J clin Path* 23, 1199
Strom, J (1951) *Acta med scand* 139 244
Wettingfield, R F , Rowe, J , Eyles, D E (1956) *Ann intern Med* 44, 557
Wising, P (1952) *Nord Med* 47, 563
von Zeipel, G , Lander, L A (1951) *Acta path microbiol scand* 29, 229

people. The measurement of reaction time provides a quantitative index of impaired cerebral function and is useful in the diagnosis of suspected hypothyroidism and in the assessment of response to therapy.

I wish to thank Prof E. J Wayne for his continued encouragement and advice, Dr J Crooks for his assistance during this study, Dr R A Robb for the statistical analysis of the results, and Dr J M A Lenihan for arranging for the construction of the apparatus.

REFERENCES

Evans, C. L. (1947) Principles of Human Physiology London.
Forbes, G (1945) *J exp Psychol.* 35, 153
Gantt, W H., Fleischmann, W (1948) *Amer J Psychiat* 104, 673
Lambert, E. H., Underdahl L. O, Beckett, S, Mederos, L. O (1951) *J clin. Endocrin.* 11, 1186
Murray, I P C., Simpson, J A. (1958) *Lancet* i, 1360
Reitan, R. M. (1953) *Arch. Neurol. Psychiat, Chicago*, 69, 436

MOVEMENTS OF THE COMMON BILEDUCT IN MAN

STUDIES WITH THE IMAGE INTENSIFIER

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For many years the method by which bile enters the duodenum has been of great interest to the physiologist and the clinician Most studies, however, have been concerned with the mechanism of emptying of the gallbladder and its functional relationship with the sphincter at the distal end of the common bileduct Little attention has been paid to any active part which might be played by the common bileduct, which is usually considered to be a transmitting tube with a wall mainly composed of fibrous tissue.

In 1889, soon after Oddi's pioneer work, Copeman reported studies on a patient with a complete external biliary fistula associated with a stone which had completely occluded the common bileduct at its distal end He noted that the secretion of bile was not continuous, but that there were "short periods of rest, followed by a flow in a series of jerks, which appeared to be caused by waves of peristaltic contraction" This hint of peristalsis in the common bileduct was followed by Mirizzi (1940), who described possible peristaltic movements in the duct and demonstrated contraction of a sphincter at the distal end of the common hepatic duct. These observations were made from a study of operative cholangiograms This work has not been confirmed

It occurred to us that it might be possible to study the common bileduct under more physiological conditions in the unanæsthetised patient by using image intensification, which would permit fluoroscopic screening with the additional possibility of recording the findings by cineradiography We have so far been unable to make any satisfactory observations by using intravenous cholangiography, owing to difficulty in obtaining definition of the biliary tract of sufficient intensity for satisfactory screening However, studies have been made after surgical exploration by the direct injection of a radio-opaque contrast medium into the common bileduct. We describe here the peristaltic movements which we have seen in the common bileduct in 10 patients after cholecystectomy

Methods and Results

The biliary tree was examined radiologically with an image intensifier one or two weeks after cholecystectomy or choledochotomy A water-miscible contrast medium, 50% or 70% sodium acetrizoate, was instilled at the rate of 1 ml a minute into the common bileduct The injection was made through a ureteric catheter which had been inserted at operation for a distance of about 1 cm. into the common bileduct through the stump of the cystic duct. If the common bileduct had been explored, the injection was made through a short T-tube left in the common bileduct at operation An initial injection of 3 ml was made. Screening was done at this time to observe the filling of the duct As the duct emptied into the duodenum, further increments of the same or less volume were instilled, the amount being determined by the rate of emptying No disturbance was experienced by the patient, and no distension of the common bileduct was allowed to take place at any time. Observations were made both during the injection and afterwards After 5–10 minutes for stabilisation of conditions in the duct permanent records were made on 35-mm film by cineradiography with a built-in 'Arriflex' camera so arranged that screening and cineradiography could be done simultaneously It was found suitable to take the film at a rate of 16 frames a second

Ten patients were studied, similar findings being made in each case

Movements of Common Bileduct and Duodenum

Four different types of movement were observed in the bileduct and the related portion of the duodenum Details of these movements were more obvious in thinner patients because visualisation was easier

Peristalsis of Common Bileduct

We observed waves of peristalsis in the common bileduct in all ten patients studied, whether or not the common bileduct was intact or had been previously explored The peristaltic waves travelled towards the duodenum at the rate of 3–5 or more a minute and lasted 1–3 seconds On one occasion 5 waves were seen in 36 seconds Sometimes a minute or more elapsed without a contraction Not all of the waves were complete and brought the medium into the duodenum, some were abortive, ending near the sphincter, but, when a wave travelled the whole length of the duct, the medium was ejected forcibly into the duodenum, and a successful complete wave was usually followed by several more At the end of a phase of peristalsis a well-marked retraction was seen at the lower end of the duct, which changed from a slender tapering channel to a shorter wider one with what appeared to be a blunt and almost rectangular tip This appearance is similar to that produced by an injection of morphine. These peristaltic movements are seen in ducts which are not under increased pressure and are not being injected with contrast medium at the time of observation

The supraduodenal angle of the duct is a suitable point for orientation when screening This point is situated just distal to the junction of the cystic and common bileducts Distal to the angle the common bileduct changes direction to run downwards and slightly laterally to its termination When contrast medium first enters the common duct through the cystic-duct stump it runs distally towards the duodenum Some minutes later it fills the common hepatic and the right and left hepatic ducts This initial distal movement may be of no significance and result from flow along a distally directed catheter On the other hand, it may support the suggestion made by Mirizzi (1940) that a sphincter is present at the to be made for the effects of practice, which Forbes (1945) and others have demonstrated

Mental sluggishness, lethargy, impaired memory, and lack of concentration are common complaints of patients with frank myxœdema, and even mild cases of hypothyroidism may be present with symptoms of this type Since the reaction time reflects higher mental processes (Evans 1947), it is not surprising to find it lengthened in myxœdema In a few patients with gross mental apathy resulting from hypothyroidism the test was made more difficult as a result of their inability to understand the instructions In many of the other cases the diagnosis of hypothyroidism could only be made after full investigation, including the response to a therapeutic trial In such patients the mental and physical slowing is much less, and it is often this which gives rise to diagnostic difficulty However, in 46 of these 50 patients the reaction times were prolonged The possibility that the anæmia which may be associated with myxœdema might play a part in the prolongation of the reaction time was eliminated by the finding of normal reaction times in severely anæmic patients

The 4 myxœdematous patients who had reaction times within the normal ranges are of special interest One was an electric welder, a skilled occupation which involved quick and rapid movements of the hands, and he had noted that he was not producing such good work as formerly The reaction time of another of these patients lay just within the upper limit of the normal range, but, when she became euthyroid, her " normal " reaction time lay below the lower limit of the normal range, suggesting that there had originally been a considerable prolongation The 2 other patients had only recently become hypothyroid as a result of radio-iodine therapy It seems possible, from these and other patients studied subsequently, that the hypothyroid state must be present for some time before the reaction time increases

When the diagnosis of hypothyroidism is obvious on clinical grounds, there is no need for further investigation, confirmation being obtained by the response to specific therapy For the investigation of cases in which the clinical picture is atypical or incomplete numerous tests have been described, but only a few have been generally adopted In such difficult cases, however, the results even of these investigations may be of doubtful significance—e g, radio-iodine studies on patients partially treated Similarly, electrocardiograms and estimations of serum cholesterol levels and B M R are often helpful but may at times give equivocal results I therefore suggest that, in cases of suspected myxœdema, the measurement of reaction time is a simple and rapid aid to diagnosis which causes minimal inconvenience to the patient Moreover, a useful index of the response of the patient to therapy is provided by the improvement in reaction time In general this parallels the changes in the clinical picture, the B M R, and the cholesterol level (fig 4) One patient stopped therapy on her own initiative, and her reaction time, which had remained within the normal range for five months when she was euthyroid, again became prolonged

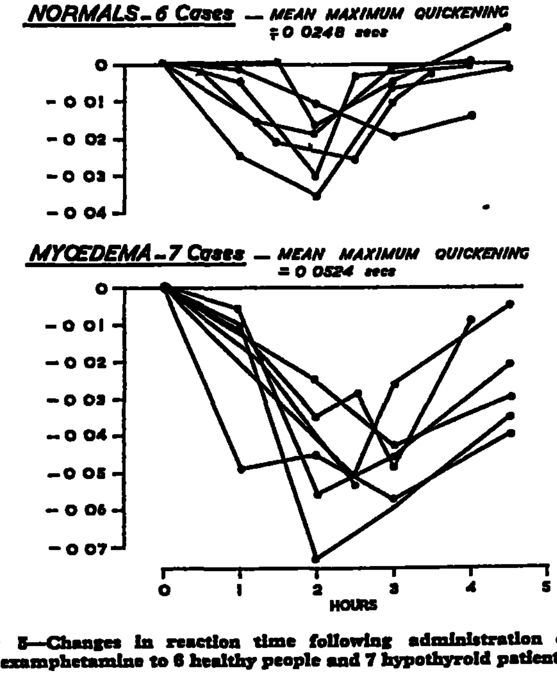

Fig 5—Changes in reaction time following administration of dexamphetamine to 6 healthy people and 7 hypothyroid patients

The changes in reaction time in myxœdema probably reflect the changes in cerebral function The results are comparable with those of Gantt and Fleischmann (1948), who studied the conditioned-reflex function in a cretin and showed that, after successful therapy, there was an improvement which reached a level in two months but did not change further over two years Other workers have studied the changes in cerebral function in myxœdema, using recognised psychological techniques, and have found evidence of impairment—e g, Reitan (1953), who used the Rorschach test Further evidence that the effect is on the higher centres is provided by the results of the studies of the effect of dexamphetamine sulphate (fig 5) After the administration of this cerebral stimulant there was a definite quickening of reaction time in healthy people When it was given to myxœdematous patients, the quickening was much greater and lasted considerably longer The possibility arises that the impairment of reaction time might be influenced by delay in the peripheral component of the arc, but this is unlikely in view of the findings of Murray and Simpson (1958), who showed that the conduction velocity in peripheral nerves was not appreciably altered in hypothyroidism Similarly, Lambert et al (1951) concluded that, although the total time taken for the ankle-jerk in myxœdema was increased, there was no appreciable difference in the speed of conduction through the reflex arc in healthy people and in myxœdematous patients They emphasised that this reflex took place over a two-neurone arc which does not involve the more complex activity of the central nervous system, as does the reaction-time pathway The estimation of reaction time therefore provides a quantitative index of one aspect of mental activity which is not only more accurate than many conventional tests but also is more easily applied and more readily adaptable to routine clinical use

Summary

By a simple and rapid method reaction times were estimated in 101 healthy people, 50 patients with hypothyroidism, and 10 patients with severe anæmia

In 46 of the hypothyroid patients, the reaction time was prolonged Specific therapy in 25 of these led to quickening of the reaction time, which returned to normal in 24, paralleling the changes in B M R and serum-cholesterol levels

Dexamphetamine shortens the reaction time of hypothyroid patients to a greater extent than that of healthy

observed peristaltic and respiratory movements of the common bileduct was possible after some of the contrast medium had entered the duodenum from the duct As has been described above, the duodenum and the common bileduct move together during respiration In addition, forward and reverse peristalsis is clearly seen in the duodenum itself We have not found that this peristalsis plays an active part in emptying the duct No duodenal movement is usually seen while the duct is expelling its contents in jets through the duodenal papilla, nor does any active duodenal contraction precede this But duodenal peristalsis usually begins after one or more waves of bileduct contraction This peristalsis is initially in the reverse direction, so the contrast medium is swept upwards towards the first part of the duodenum and the pylorus This movement is followed by forward peristalsis This succession of duodenal contractions would be expected to lead to efficient mixing of food, bile, and pancreatic juice in the second part of the duodenum

Previous observations on the functional relationship of the intraduodenal portion of the common bileduct to movements of the duodenum were made by Lueth (1931) and Long (1942) Both made their experimental studies on dogs, and both thought that the sphincteric region and the duodenal wall usually acted together Lueth thought that the intraduodenal portion was capable of independent action Our own finding that the duct empties into the duodenum while the duodenum is relaxed confirms a similar finding by Lueth It also supports the concept of an integrated functional relationship between the common bileduct and the duodenum, in that a true peristalsis (by the definition of Bayliss and Starling) in the common bileduct is preceded by a relaxation in the duodenum before the peristaltic wave reaches it

Histological Structure of Common Bileduct

It is commonly believed that the common bileduct in man is a fibrous structure containing no muscle except at its termination Standard textbooks of anatomy do not agree on its histological structure Brash and Jamieson (1937) briefly describe it as agreeing with the gallbladder in structure Johnston and Whillis (1954) say that the fibrous coat of the duct is "composed of strong fibro-areolar tissue, with a certain amount of muscular tissue, arranged, for the most part, in a circular manner" On the other hand, Grant (1940) feels that "the extrahepatic ducts are fibrous tubes containing many elastic fibres but without a muscle coat" This opinion is also held by Kozoll et al (1957), who describe the wall of the duct as consisting of "a meshwork of interlacing collagen and elastic fibres . smooth muscle is only seen in the intra-duodenal segment"

Burden (1925) reported on the structure of the supraduodenal portion of the common bileduct, basing his description on a study of 100 necropsy specimens He found that the bileducts were supplied with a well-developed musculature The muscle was situated in the outermost layers of the wall, both in longitudinal and circular bundles, the former being the more notable Burden could not find a published description of peristalsis in the human bileduct but thought it possible from its structure

Our observations on the supraduodenal bileduct in man show that there is indeed an interlacing network of collagen and elastic fibres in the wall as described by Grant (1940) and Kozoll et al (1957), but there is smooth-muscle tissue in the duct (fig 3) varying in amount with the individual, the muscle-fibres interdigitating with collagenous and elastic tissue

Discussion

We have shown that peristaltic movements occur in the common bileduct in man, and we are convinced that the anatomical basis for this is present

Following these observations, we have begun a comparative study of histological structure and biliary-tract movements in animals We have confirmed that obvious peristalsis can be seen under anæsthesia where there is muscular tissue in the duct wall The occurrence of peristalsis is not related to the presence or absence of a gallbladder in the species concerned (unpublished observations)

Peristalsis has not been described in the common bileduct at operation, but this need not imply that it does not occur under physiological conditions At operation the effect of the drugs used for premedication and for anæsthesia may be sufficient to reduce or to abolish movements, the length of bileduct actually exposed and available for study is usually short, and it is rare for a healthy duct to be closely examined We have studied movements of the duct only after cholecystectomy, perhaps they occur as a compensatory mechanism after cholecystectomy However, the gallbladders removed before the radiological studies in this series had obviously been functionless for many months

As a result of this study we believe that the common bileduct functions as an actively contracting duct rather than as a passive transmitter of bile This concept may modify current views on the genesis of biliary pain and permit the consideration of common bileduct colic as

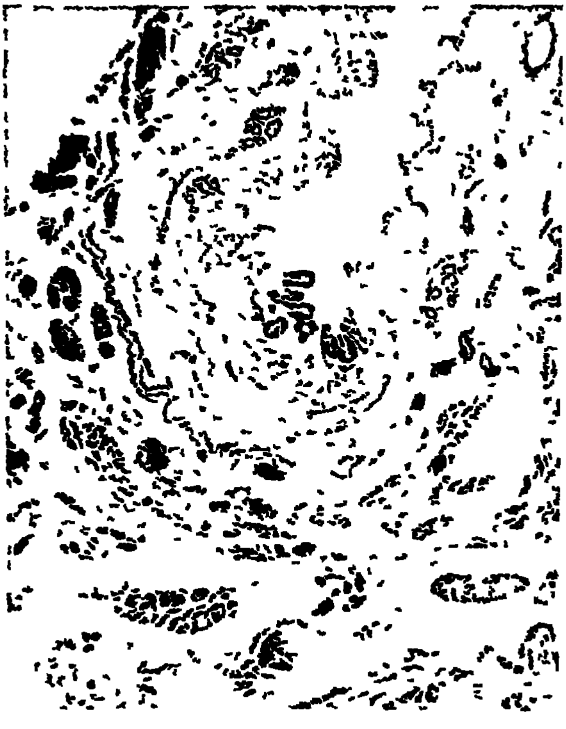

Fig 3—Cross-section of distal quarter of human common bileduct proximal to intraduodenal portion Smooth muscle is present, chiefly in outer coat Muscle bundles are mainly longitudinal but there are some oblique and circular fibres Mucosa has been almost completely destroyed by autolysis (Hæmatoxylin and eosin. ×40)

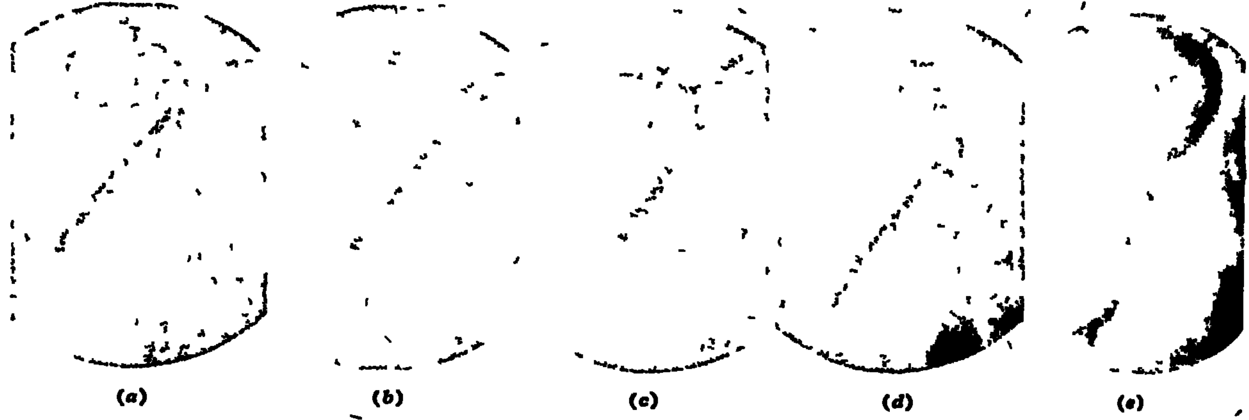

Fig 1—Stages in peristaltic waves in distal common bileduct, from cineradiographic film of biliary tract of woman, aged 38, who underwent cholecystectomy 10 days earlier Times between photographs a–b, 4 9 sec , b–c, 2 3 sec , c–d, 2 9 sec , d–e, 8 0 sec

distal end of the common hepatic duct Mirizzi's argument is supported by cholangiograms made during operation, which show extreme narrowing of the main bileduct at the junction with the cystic duct These may possibly represent movements of maximal contraction during a peristaltic wave, but in this region of the duct the peristaltic waves which we have seen do not cause complete obliteration of the duct They can be described as ripples progressing distally, which can be clearly identified but do not completely occlude the duct Distal to the supraduodenal angle the contractions are greater, making greater indentations in the duct wall as the peristaltic wave passes along

These peristaltic waves can be seen easily on screening and have been reproduced by cineradiography It has not proved possible to illustrate them completely by serial reproductions from a film strip, but some aspects can be seen in figs 1 and 2 taken from a cineradiographic film of the bileduct of a female patient, aged 38, who underwent cholecystectomy for gallstones 10 days earlier At operation the common bileduct appeared normal, and this was confirmed by operative cholangiography The duct was not explored In figs 1 and 2 a ureteric catheter can be seen entering the common bileduct through the stump of the cystic duct Through this catheter 70% sodium acetrizoate was injected into the common duct

Fig 1 shows various stages in peristaltic waves which have reached the distal common bileduct The medium can be seen entering the empty duodenum Comparison of fig 1a and fig 1d, with reference to the relation of the supraduodenal angle of the duct to the vertebræ, shows the extent of normal respiratory movement

Fig 2 shows the considerable change in the appearance of the same duct 20 minutes later Various stages in waves in the distal portion of the duct are reproduced for comparison with fig 1 In addition fig 2d shows the appearance of the duct in its resting or nonperistaltic state at the completion of a wave 5 7 seconds after the exposure of fig 2a The appearance of the duct in fig 2d is very like that seen after a subcutaneous injection of morphine

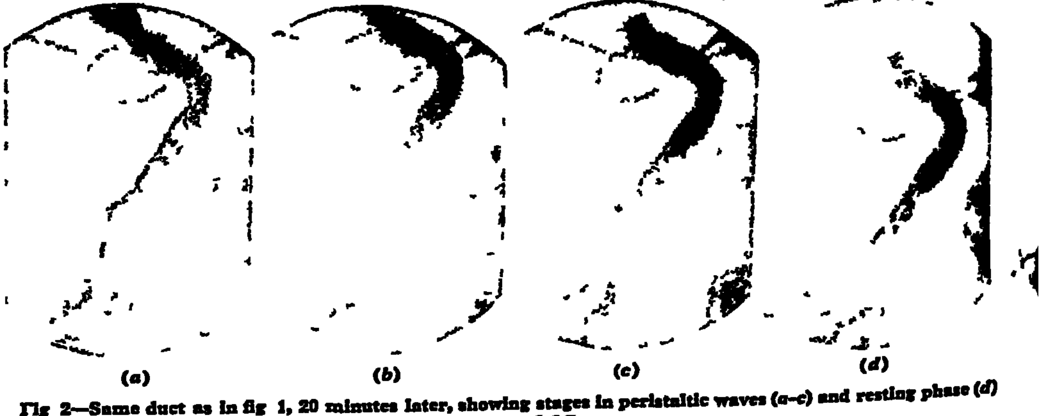

Fig 2—Same duct as in fig 1, 20 minutes later, showing stages in peristaltic waves (a–c) and resting phase (d) Times between photographs a–b, 2 1 sec , b–c, 1 sec.; c–d, 2 7 sec.

Respiratory Movement

The whole biliary tree moves with each respiratory excursion, a downward movement in inspiration is followed by a return upward movement in expiration The bileduct and the duodenum move together, but the ejection of contrast medium into the duodenum is not in any way associated with these movements In common with many other workers we have observed, by simple manometry, that pressure changes occur in the common bileduct during each respiratory cycle—normally about 1 or 2 cm of bile These minor but definite rises in pressure can be considerably increased by deep inspiration or by coughing, but they do not appear to contribute to the emptying of the common bileduct, because the emptying of the duct into the duodenum is not regularly related to the observed respiratory movement or significantly increased by deep inspiration or by coughing

Transmitted Arterial Pulsation

In a patient with a thin abdominal wall it is possible to see, on screening, that the common bileduct pulsates synchronously with the aorta This is not surprising, because the aorta and the cœliac axis are close to the duct, and the hepatic artery runs in intimate relationship with the duct, hence transmitted pulsation may be expected This movement is of minor degree and has no bearing on the emptying of the duct

Associated Duodenal Movements

A study of duodenal movements in relation to the

FOURTEEN CASES OF MALABSORPTION SYNDROME

Clinical grade	Case no	Age (yr)	Sex	Diagnosis	Fat excreted in fæces in 24 hr (g)	Loss of weight (lb)	Hg (g per 100 ml)	Serum-albumin (g per 100 ml)	Serum-potassium (mEq per litre)	Serum-sodium (mEq per litre)	% of fluid excreted in 4 hr		
											Intravenous fasting	Oral fasting	Oral non-fasting
I	1	32	M	Crohn's disease, ileal resections (1955 and 1957)	15	6	14·8	4·6	3·9	132	47	73	84
	2	33	M	Idiopathic steatorrhœa in remission on gluten-free diet	13	Nil	13·6	4·0	3·9	140	60	38	126
	3	54	F	Partial gastrectomy (1957)	14	7	14·0	4·4	—	—	91	83	64
	4	71	M	Jejunal diverticulosis	19	Nil	14·0	3·8	3·9	127	120	81	24
	5	19	M	Crohn's disease of ileum	12	9	12·0	4·4	4·0	136	47	58	96
II	6	51	M	Idiopathic steatorrhœa, compensated hepatic cirrhosis	65	14	12·2	2·2	3·4	130	63	56	75
	7	55	M	Tuberculous ileocolitis, rt hemicolectomy (1951), resection of blind loop (1956)	35	28	12·5	4·0	3·8	147	76	48	—
	8	60	M	Partial gastrectomy (1949), osteomalacia and osteoporosis	10	28	12·6	4·2	4·5	135	51	80	46
	9	61	M	Total gastrectomy for peptic ulcer and œsophageal stricture (1957)	15	28	12·2	2·8	3·5	135	46	70	60
III	10	41	M	Crohn's disease, rt. hemicolectomy (1950), partial gastrectomy (1955)	50	35	10·1	3·3	4·5	135	8	8	13
	11	38	F	Crohn's disease of ileum	24	21	8·8	2·7	3·6	147	16	13	—
				(3 weeks after treatment)	6	Gained 14	10·2				112	91	67
	12	72	M	Idiopathic steatorrhœa	15	42	13·0	3·2	2·5	130	18	28	17
	13	51	M	Total gastrectomy (1956), carcinoma of jejunum	33	51	10·1	4·5	2·4	147	16	10	—
	14	62	M	Partial gastrectomy (1951)	8	21	8·9	3·3	4·5	127	40	27	34

Results

All the patients with steatorrhœa had impaired diuresis compared with the controls both when the water loads were given orally (fasting or non-fasting) or when they were given intravenously in the fasting state. Cases 1–5 and 8 achieved diuretic responses within the normal range but not under all three test conditions. In patients with steatorrhœa there was a wider range of response under all the test conditions than in the controls. The mean excretion of fluid after each method of giving the water load was between 48–58% in the patients with steatorrhœa and 100–114% in the controls (fig. 1). Fasting did not influence the diuretic responses to oral water loads in the patients with steatorrhœa.

The diuresis was subnormal not only in the patients with idiopathic steatorrhœa but also in those with malabsorption due to total or partial gastrectomy, Crohn's disease, tuberculous enteritis, or jejunal diverticulosis (see table). There was a correlation between the impairment of diuresis and the severity of the disease, the mean excretions in the three test conditions being grossly impaired in grade-III patients and relatively intact in grade-I patients (fig. 2). In case 11 diuresis improved three weeks after treatment, in keeping with the clinical improvement (see table).

The hæmoglobin level was 12 g. per 100 ml. or below in 5 patients, the anæmia being macrocytic in 3, normocytic in 1, and due to iron-deficiency in 1. The anæmia was severest in grade-III patients, thus being associated with defective diuresis. There was no relationship between the degree of steatorrhœa and the diuresis (fig. 3).

Clinical and radiological evidence of intestinal distension was present in cases 4, 6, 7, 13, and 14. "Steatorrhœa" patterns were found in cases 2–4, 6, 8, and 10–14. There was therefore no relationship between impaired diuresis (see table) and the degree of distension of the small intestine or other radiological appearances.

Serum-potassium levels were low in some patients,

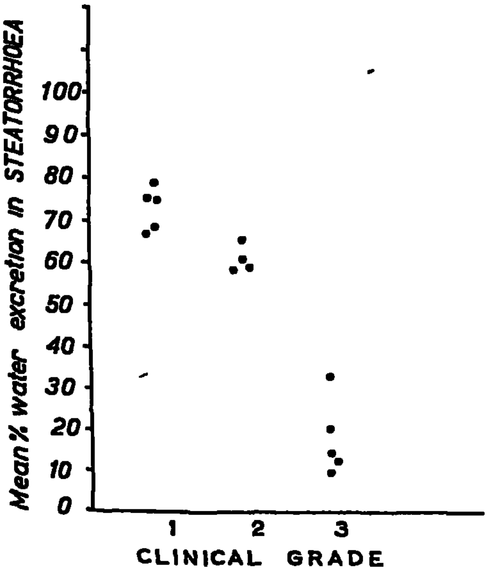

Fig. 2—Excretion of fluid in relation to clinical condition.

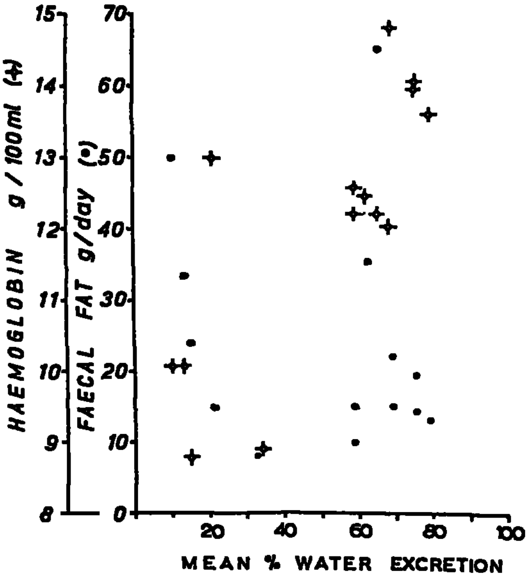

Fig. 3—Excretion of fluid in relation to severity of anæmia and of steatorrhœa.

an entity similar in nature to ureteric and intestinal colic

Summary and Conclusions

By image intensification and cineradiography we demonstrated peristaltic movements in the common bileduct in man after cholecystectomy

The waves of peristalsis were directed distally along the duct towards the duodenum and propelled bile into the duodenum

Respiratory and duodenal movements were also studied, they played no great part in emptying the bileduct under the conditions of our observations

We believe that there is sufficient muscle in the wall of the bileduct to produce these observed rhythmic movements, and conclude that this intrinsic muscle is responsible

We thank Professor Illingworth and Dr Scott Park for providing facilities to make this study, and the radiographers of the Western Infirmary, Glasgow, for their cooperation

REFERENCES

Brash, J C, Jamieson, E B (1937) Cunningham's Text-book of Anatomy London

Burden, V G (1925) *Coll Pap Mayo Clin* 17, 107

Copeman, S M (1889) *Lancet*, i, 1026, 1075

Grant, J C B (1940) A Method of Anatomy London

Johnston, T B, Whillis, J (1954) Gray s Anatomy London

Kozoll, D D, Schaffner, F, Potter, H (1957) *in* Physiologic Principles of Surgery (edited by L M Zimmerman and R Levine) London

Long, H (1942) *Brit J Surg* 29, 422

Lueth, H C (1931) *Amer J Physiol* 99, 237

Mirizzi, P L (1940) *Arch Surg* 41, 1325

EXCRETION OF FLUID IN MALABSORPTION STATES

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Disordered metabolism of water in idiopathic steatorrhœa is suggested by the tendency to œdema of the ankles and nocturnal polyuria Wollaeger and Scribner (1951) showed that, after an oral water load in such patients, diuresis was impaired in the non-fasting state but not when the patients were fasting They therefore concluded that the presence of food, with pooling of fluid in the intestines, delayed the absorption of water and consequently retarded its excretion Taylor (1955a), however, could not improve the defective diuresis by fasting in idiopathic steatorrhœa

We report here diuretic responses to water loads in various malabsorption states, including idiopathic steatorrhœa In particular we compare the effects of intravenous and oral loads given to fasting and non-fasting persons

Materials and Methods

We studied 14 patients with malabsorption syndromes (see table) 3 had idiopathic steatorrhœa, 4 regional ileitis (including 2 with resections of small intestine), 1 tuberculous enteritis followed by resection of terminal ileum, 1 jejunal diverticulosis, and 5 steatorrhœa following total or partial gastrectomy The fæcal fat averaged more than 5 g per twenty-four hours over three days on varied ward diets, thus conforming with Cooke's (1956) criteria for steatorrhœa Additional diagnostic investigations, by standard methods, included examination of peripheral blood and sternal marrow, estimations of serum-protein and serum-electrolyte levels, radiological studies of the alimentary tract and bones, surgical or aspiration biopsies of the small intestine, and oral glucose-tolerance tests

The patients were divided into three clinical grades of severity judged particularly by loss of weight and by disability grade I, mild or in remission, grade II, moderately active disease, grade III, severe relapse requiring admission to hospital (see table)

In no patient did the history, clinical findings, specific gravity and routine analysis of the urine, or blood-urea level suggest renal disease

We studied as controls 19 persons, of comparable age and sex, recruited from hospital staff and patients None had evidence of renal, hepatic, cardiac, endocrine, or gastrointestinal disease with the exception of peptic ulcer

The subjects received oral tap-water loads (20 ml per kg of body-weight) under fasting and non-fasting conditions and intravenous water loads as 5% dextrose (15 ml per kg of body-weight) in the fasting state For fasting tests nothing was allowed by mouth after 10 P M the previous night After the bladder had been emptied next morning, the fluid was given within forty-five minutes, and the output of urine over the next four hours was measured Non-fasting tests were made after the midday meal but otherwise with the same routine The patients were recumbent during the tests, and the volume of urine was recorded as a percentage of the intake of fluid under each of the test conditions The mean percentage of the fluid loads excreted was calculated from the volume of urine excreted in four hours after the three tests

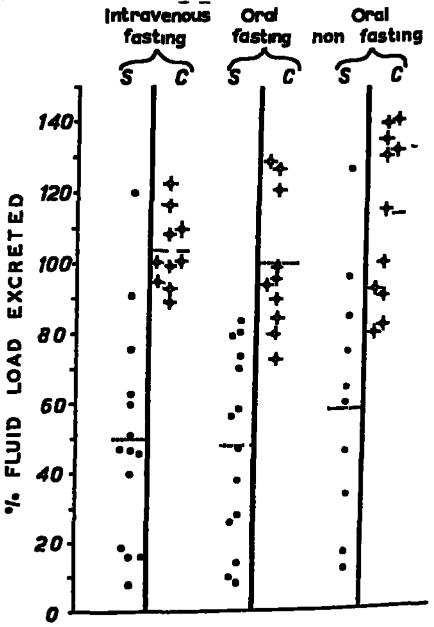

Fig 1—Excretion of fluid by patients with steatorrhœa and by controls
S = steatorrhœa C = control Interrupted transverse line = mean excretions

HÆMORRHAGIC PLEURAL EFFUSION AS A MANIFESTATION OF SCURVY

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SCURVY in Great Britain is not as rare as previously believed (Thompson 1954, Cutforth 1958) The clinical manifestations now encountered differ greatly from the textbook descriptions

Case-report

A joiner's labourer, aged 62, was seen by one of us (W R) on April 24, 1957, at his home with six weeks' history of right pleural pain and increasing dyspnœa He was admitted the same day to Primrose Hill Hospital, Jarrow on Tyne

In October, 1954, he had had epigastric pain between meals, relieved by alkalis and vomiting A barium meal examination that year showed a large gastric ulcer on the lesser curve extending into the posterior wall The chest radiograph was then normal

First previous admission—In January, 1955, he had been admitted to another hospital for treatment of his peptic ulcer His hæmoglobin (Hb) was 101%, leucocyte-count 8800 per c mm (normal differential count), urine normal, Wassermann reaction and Kahn test negative, fæcal occult blood present in one of six specimens He was treated with diet, alkalis, and iron, and discharged improved at the end of five weeks to continue with the same treatment and to attend for review as an outpatient On March 3, 1955, barium meal did not show the previously noted ulcer crater The chest radiograph was again normal

Second previous admission—On June 7, 1956, he was admitted as an emergency with a month's history of increasing effort dyspnœa and left pleural pain He looked ill and was cyanosed and dyspnœic, with signs of a left pleural effusion A chest radiograph (fig 1) on the same day showed a left pleural effusion, and aspiration yielded 20 ml of grossly bloodstained fluid which was sterile on culture The blood-urea was 36 mg per 100 ml, liver-function tests were normal, plasma-proteins 6 15 g per 100 ml, sputum negative for tubercle bacilli, no occult blood in fæces, Hb 47%, no evidence of iron deficiency on blood-film, and erythrocyte-sedimentation rate (E S R) 115 mm in the first hour (Westergren) He was treated with vitamins ('Abidec') and intravenous iron ('Ferrivenin'), and the chest was aspirated on several occasions, grossly bloodstained fluid being obtained each time He was discharged on Aug 1, 1956, clinically improved but still with a left pleural effusion In view of the history of gastric ulcer, malignancy with pulmonary metastases was suspected, and he was asked to attend for outpatient review When he was seen on Sept 18, his condition was found to be satisfactory and he defaulted from further attendance

Course—Four months before admission in April, 1957, he ceased work on account of general malaise followed by pain in the right loin and a series of upper respiratory infections He remained in bed for three weeks Six weeks before admission he complained of severe right pleural pain which persisted, increasing dyspnœa, and generalised weakness His diet since the onset of his ulcer symptoms (October, 1954) had consisted mainly of carbohydrates and boiled fish, with the exclusion of meat and vegetables, and he had received no additional vitamins since his discharge from hospital in August, 1956 There was no family history of blood dyscrasias

On admission (April 24, 1957) he was ill and dyspnœic with signs of a right pleural effusion There were splinter hæmorrhages under the nails of both hands, a few small bruises on the left leg, and considerable bruising and swelling of the right lower leg He had no teeth and his gums appeared healthy

Investigations—The pleural fluid was grossly bloodstained and sterile on culture, subsequent examinations showed Hb 24–34% in the fluid In the blood, the Hb was 60% (8 9 g per 100 ml), erythrocyte-count 3,410,000 per c mm (colour-index 0 9), and leucocyte-count 4600 per c mm, the red cells showed mild anisocytosis and hypochromasia The bleeding-time was 2 min, Hess' test negative, and prothrombin-time normal The Wassermann reaction and Kahn test were negative, the E S R (Wintrobe) was 52 mm (uncorrected) or 28 mm (corrected for anæmia) in the first hour Fæces (three specimens) contained no occult blood A chest radiograph on admission showed a large right pleural effusion, the left side was clear (fig 2) An ascorbic-acid saturation test showed no excretion until the seventh day

Treatment and further observations—He was treated by repeated chest aspirations, oral iron, and large doses of ascorbic acid His general condition improved quite rapidly, the skin hæmorrhages faded, and his effusion lessened (fig 3) In view of the previous suspicion of malignancy he was transferred for special investigation to Holywood Hall Hospital on Jan 13, 1957 Bronchoscopy (Mr W C Barnsley) was normal A bronchogram showed some crowding and bronchiectasis of the posterior basic segment of the right lower lobe Pleural fluid was reported as containing "several clumps of cells almost certainly neoplastic" An electrocardiogram was normal Hb 83%, platelets not diminished, clotting-time 10 min 15 sec, bleeding-time 4 min 20 sec He was discharged home on July 13

Follow-up—Since his discharge he has been followed up by one of us (W R.) and a chest radiograph on Aug 7 showed that the effusion had completely cleared He continues to have indigestion, and is keeping to his diet but having vitamin supplements When he was last seen on March 3, 1958, his chest radiograph (fig 4) showed a shallow right costophrenic

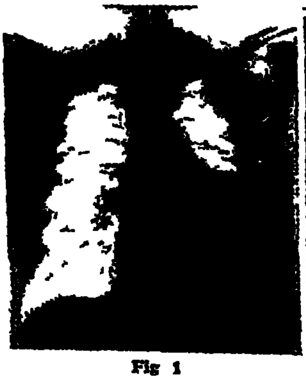

Fig 1

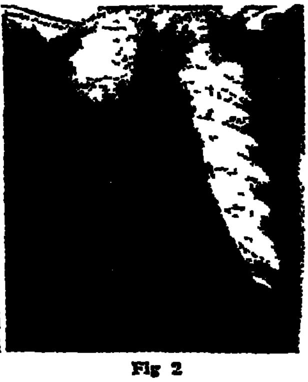

Fig 2

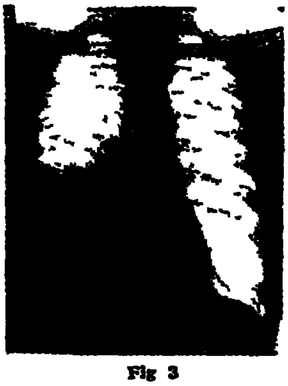

Fig 3

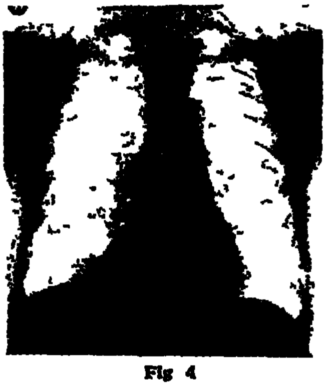

Fig 4

Fig 1—June 6, 1956 left pleural effusion
Fig 2—April 24, 1957 right pleural effusion
Fig 3—May 31, 1957 right pleural effusion, less than in fig 2.

Fig 4—March 3, 1958 lung fields clear except for slight pleural thickening in right costophrenic angle and crowding of bronchi in right lower zone

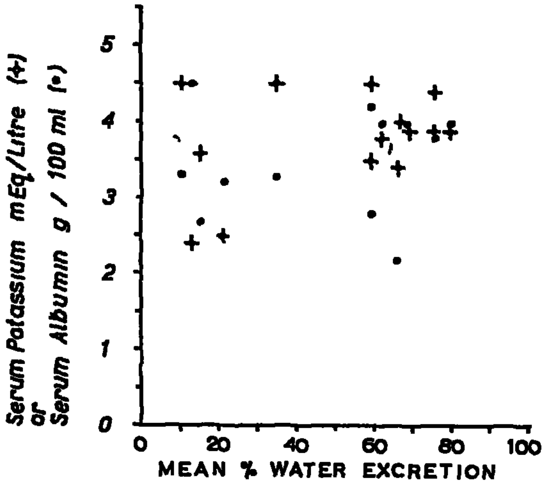

Fig 4—Excretion of fluid in relation to serum-potassium and serum-albumin levels

more particularly those who were more severely ill, but no relationship with diuresis was apparent Similarly, impairment of diuresis was not related to the degree of hypoalbuminuria (fig 4)

Specimens of upper jejunum were obtained from 10 patients with steatorrhœa (in case 6 at laparotomy, in case 13 at necropsy, and from 8 patients by aspiration biopsy) Diuresis was not directly related to either the presence or the absence of mucosal changes, because biopsy specimens from cases 3, 4, 6, 8, and 14 were normal, and those from cases 2, 7, 11, and 12 showed mucosal atrophy

Nocturnal polyuria, with or without œdema of the ankles, was pronounced in cases 7 and 9 (grade II) and 10, 12, and 13 (grade III)—i e, in association with more severe impairment of diuresis

Discussion

Impaired absorption of water, due to the pooling of fluid in the gut during the digestion of food, was emphasised by Wollaeger and Scribner (1951) as the cause of the delayed diuresis in idiopathic steatorrhœa, but we, like Taylor (1955a), found comparable impairments in diuresis under both fasting and non-fasting conditions Furthermore, clinical and radiological evidence of intestinal distension with fluid levels and gas was unrelated to the efficiency of diuresis in our patients

Nevertheless, studies with isotopes have confirmed that the absorption of water from the small intestine is delayed in idiopathic steatorrhœa (Higgins et al 1957) This could theoretically be due to lesions of the small-intestinal muscosa (Paulley 1954, Shiner 1957) Mucosal changes in the small intestine are also present in Crohn's disease and tuberculous enteritis, and they may follow partial gastrectomy (Baird and Dodge 1957) Impaired diuresis, in the present study, was a feature of all these conditions, but it could not be related directly to the severity of the histological lesions found in the small gut, and subnormal responses to water loads were obtained in the absence of demonstrable mucosal changes

A similar impairment of diuresis after the intravenous administration of fluid suggests that altered renal excretion of water was a more important factor than intestinal malabsorption Simple dehydration is unlikely to explain the impaired diuresis, because the same delays in excretion were found in both fasting and non-fasting states, and in most patients there was no watery diarrhœa or other cause of dehydration

Patients with more active disease exhibited the greatest impairment of diuresis, and, in the 1 patient studied, rapid improvement followed successful treatment A subnormal diuretic response to water loading is to be anticipated in many types of serious illness but not to the degree that was found in malabsorption states Anæmia (Taylor 1954b, 1955b) and malnutrition with or without hypoproteinæmia (Sinclair 1948) may influence the renal excretion of water to some extent In the present series severely ill patients had lost the most weight and had the greatest anæmia, but abnormal results also occurred in the absence of anæmia or of malnutrition There was no correlation between diuresis and serum-albumin levels or the amount of fat in the stools This accords with the findings of Cooke (1957), but Taylor (1954a) found a relationship between diuresis and the degree of steatorrhœa

In addition to disordered metabolism of water, faulty absorption of sodium (Newsholme and French 1954) and fæcal loss of sodium and potassium (Cooke et al 1953) have been reported in idiopathic steatorrhœa Cooke (1957) postulated that a renal tubular nephropathy due to depletion of potassium might contribute to the impaired diuresis in idiopathic steatorrhœa No evidence of kidney disease was found in the present study, but we could not fully exclude a nephropathy, and hypokalæmia was sometimes present Cooke failed to influence the diuresis by administering hydrocortisone, in contrast to the improvement coinciding with the use of hydrocortisone in a patient reported by Nabarro et al (1957) These considerations therefore indicate a profound metabolic disorder of both water and electrolytes during relapses in the malabsorption syndrome, possibly implicating adrenocortical or neurohypophyseal function and resembling the abnormal diuretic patterns in cardiac, renal, and hepatic disease

Summary

Diurésis is delayed after the administration of fluid in idiopathic steatorrhœa and in other small-intestine malabsorption states A comparable impairment of diuresis follows both oral and intravenous fluid loads in both the fasting and the non-fasting states

The degree of impairment of the response is more closely related to the severity of the clinical condition than to specific biochemical, radiological, hæmatological, or histological changes, and, as a casual factor, disordered renal excretion appeared more important than malabsorption of water from the intestine

We are grateful to Dr F Avery Jones for advice and for encouragement of these studies, Dr M Shiner for the aspiration biopsies of the jejunum, and Sister M Johnson and Sister M Spire and their nurses for preparing the patients and collecting the specimens

REFERENCES

Baird, I M, Dodge, O G (1957) *Quart J Med* 26, 393
Cooke, W T (1956) *Proc R Soc Med* 49, 627
— (1957) *J Mt Sinai Hosp* 24, 221
— Peeney, A L P, Hawkins, C F (1953) *Quart J Med* 22, 59
Higgins, J A, Lee P R, Scholer J F, Reitemeier, R J, Code, C F, Wollaeger, E E (1957) *J clin Invest* 36, 265
Nabarro, J D N, Moxham, A, Walker, G (1957) *Brit med J* ii, 1018
Newsholme, G A, French, J M (1954) *Clin Sci* 13, 607
Paulley, J W (1954) *Brit med J* ii, 1318
Shiner, M (1957) *J Mt Sinai Hosp* 24, 273
Sinclair, H M (1948) *Proc R Soc Med* 41, 541
Taylor, W H (1954a) *Clin Sci* 13, 239
— (1954b) *ibid* 13, 497
— (1955a) *ibid* 14, 725
— (1955b) *ibid* 14, 731
Wollaeger, E E Scribner, B H (1951) *Gastroenterology*, 18, 224

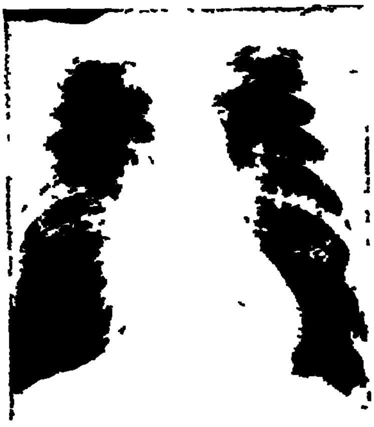

Fig. 1—Case 1: radiograph (somewhat overpenetrated) showing filling of right costophrenic angle and peaking of right diaphragm, fine nodulation of lung fields, most marked in right mid zone; linear shadows on left side not obscured by nodulation, and increased translucency at bases.

Bare wire electrodes are practically never used nowadays, coated electrodes having many advantages. The coatings act as a stabiliser of the arc, a flux, a slag to prevent too rapid cooling, a sheath to exclude air, and a source of certain elements for the weld metal. Common constituents of the coatings include oxides of iron, titanium, and manganese, silicates (such as various clays and felspar), and carbonates of calcium and other metals. The resultant fume is therefore of complicated composition, and iron oxides may constitute a relatively small proportion of it. According to Thrysin et al. (1952) a typical fume, when steel is being welded with neutral coated electrodes, may contain 30–60% of iron oxide, but with basic-coated and other special-purpose electrodes the iron-oxide content may be as low as 16%.

Other common constituents include silicates and the oxides of titanium, manganese, and calcium. The form in which silica exists in the fume does not appear to have been accurately determined, but according to Tebbens and Drinker (1941) crystalline silica is absent. It is believed that, at the temperature of the arc, any free silica that might be produced would combine with the oxides present to form silicates.

Silica and other dusts may arise from extraneous sources. For instance, electric-arc and carbon-arc welders and oxyacetylene burners or cutters working in the fettling-shops of foundries and, less often, in engineering-shops, where castings are cleaned, are exposed to the dust of free silica in the atmosphere of these shops.

Harding et al. (1950) described the pathology of the lungs of a carbon-arc welder who had worked in a steel fettling-shop. The lungs showed areas of mixed-dust fibrosis, and in the hilar glands were well-marked silicotic nodules.

McLaughlin and Harding (1956) described the necropsy and other findings in 5 welders and oxyacetylene cutters employed in iron or steel foundries for ten to thirty-seven years (average 21·2 years). Slight mixed-dust fibrosis was present in the lungs of 3 of these men but was not a factor in the death of any of them.

Charr (1955, 1956) has described the pathology of the lungs of 4 welders: 1 a complete necropsy and the 3 others lung biopsies. He showed that there was slight fibrosis in relation to the iron pigment in 3 of the cases.

Mann and Lecutier (1957) found emphysema and loss of elasticity in a lobe, excised because of a tuberculoma, from an arc welder of twenty-five years' experience whose X-ray film showed "an increase in the vascular markings, accompanied by a fine stippling of nodules 1 mm. in size, scattered mainly throughout the lower two-thirds of both lung fields." The emphysematous portion of the lung had 22% of ferric oxide and the tuberculous portion 13%. On the basis of this complicated case Mann and Lecutier suggest that iron oxide is not inert, and that arc welders' lung is not always innocent and reversible. Prof. J. Gough, who made a large section of the lung, found that the iron deposits were related to and a probable cause of the emphysema. But the larger iron content of the emphysematous portion of the lung compared with the tuberculous portion could equally be ascribed to lymphatic obstruction in the latter, limiting the entry of iron-dust particles into that portion.

We present here the pathology of the lungs of 4 electric-arc welders and 1 oxyacetylene cutter or burner who, so far as we could determine, had not worked in foundries or been exposed to the dust of free silica in other industries. In 2 of the electric-arc welders slight mixed-dust fibrosis was found, and in the other 2 there was no fibrosis, though 1 had been exposed to welding fume for forty-two years before he died as the result of an accident.

Case-reports

Case 1.—An electric-arc welder, who was 69 when he died in 1956, had always worked in engineering-shops, never in foundries. He started welding in 1914, and after 1917 always used coated electrodes usually wrapped with asbestos. He gave up welding in 1943 (after twenty-nine years) and became a club steward; he gave up all work in 1950 because of cough and dyspnœa. He was examined by a pneumoconiosis medical panel in 1950 and in 1953 and was judged to have pneumoconiosis and severe emphysema, but his total disablement was considered not to be due to pneumoconiosis. Radiography of his chest (fig. 1) on April 6, 1955, showed that his skeletal and

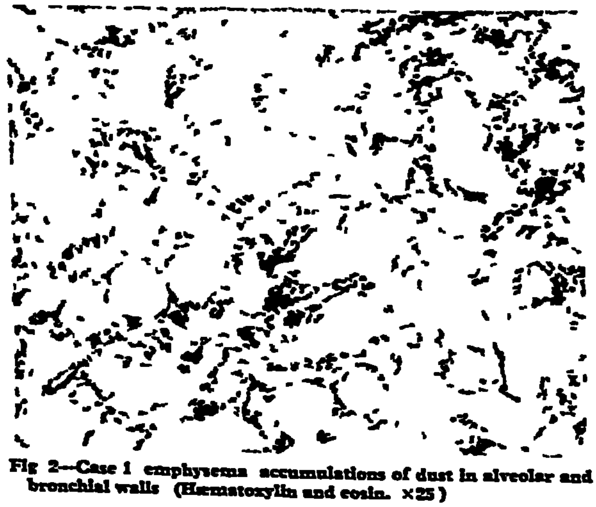

Fig. 2—Case 1: emphysema; accumulations of dust in alveolar and bronchial walls. (Hæmatoxylin and eosin. ×25.)

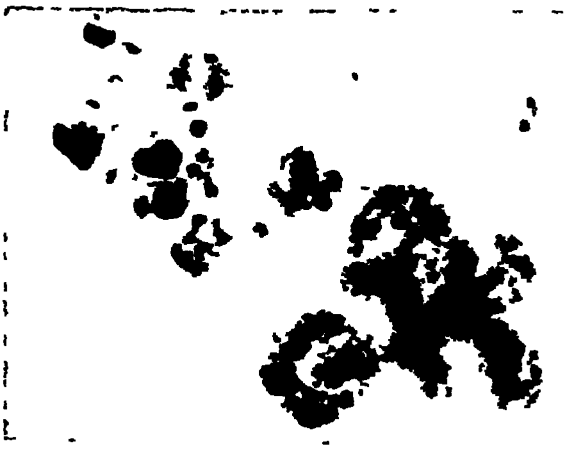

Fig. 3—Case 1: "curious body" in lung (probably an aggregate of cells containing hæmosiderin). (Hæmatoxylin and eosin. ×680.)

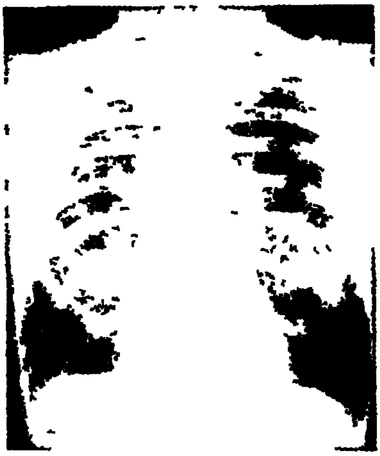

Fig 7—Case 4 radiograph of chest showing reticulation with micro-nodulation over both lung fields, more marked in mid-zones, with linear shadows obscured by the nodulation, and some increased translucency at bases

(fig 5) Apart from the bleeding, this was essentially a normal lung

Comment.—Little pigmentation and no fibrosis of the lungs were found after about forty years' electric-arc welding

Case 3—A man, aged 61, had been an electric-arc welder for more than thirty years for a city corporation, working mainly on tram-lines He collapsed and died on an omnibus After a necropsy, the cause of death was given as "myocardial fibrosis, coronary atherosclerosis"

Necropsy findings—To the naked eye the lungs were apparently normal, apart from congestion They showed only slight focal pigmentation and no fibrosis The hilar lymph-nodes were slightly enlarged, black, and soft. A large section of lung showed only the slightest traces of simple pneumoconiosis and might well be accepted as normal for a man who had lived for sixty years in a dirty industrial city (fig 6) There was slight fine emphysema, not focal in type, at the margins of the lower lobe Microscopically the lungs showed congestion and œdema with very slight mixed-dust fibrosis The hilar lymph-nodes showed a little fibrosis unrelated to pigment Chemical analysis gave, as percentages of weight of dried lung, ash 3 85, total silica 0 15, free silica 0 006, and iron (as ferric oxide) 0 5

Comment—There was insignificant fibrosis after more than thirty years' welding

Case 4—A man, aged 63, died in 1956 From 1907 to 1918 he served his apprenticeship as a boiler riveter and worked casually on ship-repair work as such until he changed over to electric welding in 1918 From 1918 to 1926 he worked on board ships, using covered rods and never doing any carbon-arc welding or gas welding For the next ten years he was a welder of boilers, and about 80% of his time would have been spent in enclosed spaces, the only precaution against fumes being the use of a compressed-air pipe to ventilate his working-compartment For the next ten years he worked to a greater extent on ship repairs, and probably only 50% of his time would have been in enclosed spaces A lot of the work would have been on painted metal, and less than 5% on galvanised metal In general the welding would not have been of heavy type, the usual current would be 200 amp, with a maximum of 300 amp and the average thickness of the electrodes would be 6-gauge.

He had pleurisy at the age of about 13 years For the last ten years of his working life he had bronchitis and had been off work several times In January, 1946, he was off work for three weeks with bronchitis, he returned to work for four days and was then ill with pneumonia He had not worked since He made a claim to the Silicosis Board in November, 1946, and was examined by the panel in January, 1947 The clinical findings then were those of an unresolved pneumonia at the right base There was no clubbing of the fingers, and his general condition and exercise-tolerance test were considered sufficiently good for him to do light work A certificate was refused Radiography in 1947 showed normal skeletal, heart, and diaphragm shadows and no increased hilar shadows, reticulation with a micronodulation throughout both lungs, mainly in the mid zones, and increased translucency at the bases suggesting emphysema Another radiograph (fig 7), taken in 1954, showed no alteration in the picture.

Necropsy findings—Dr D M McClure reported "Dense pleural adhesions are present on both sides The lungs are fairly bulky, and show well-marked vesicular emphysema without the formation of large bullæ On section the lungs show fine diffuse nodularity of fibrous type These fibrous nodules are very small and in no instance coalesce into large masses At the most they are just palpable, but they are very numerous and uniformly distributed in all areas The picture is quite distinct from that seen in typical coalminers' pneumoconiosis, but it is none the less a process of pneumoconiotic type Chronic bronchitis is also prominent The cause of death was given as chronic bronchitis and emphysema associated with fine diffuse pneumoconiotic fibrosis" Sections from the lungs show generalised emphysema and probably some focal emphysema associated with small areas of mixed-dust fibrosis in which collagen is present (figs 8 and 9)

Comment—There was slight but definite mixed-dust fibrosis in the lungs of a man who had done arc welding for twenty-eight years, mostly in enclosed spaces Whether this fibrosis played any significant part in his disability and death or not we consider to be very doubtful The main, if not the sole, cause of his disability was chronic bronchitis and emphysema Possibly these conditions may have been occupational in origin, caused by paint fumes, constituents of the rod coverings, or oxides

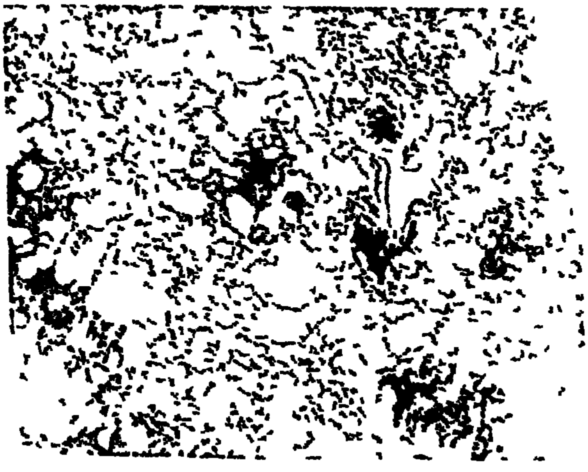

Fig 8—Case 4 small areas of mixed-dust fibrosis; emphysema, generalised and possibly also focal. (Hæmatoxylin and eosin ×8.)

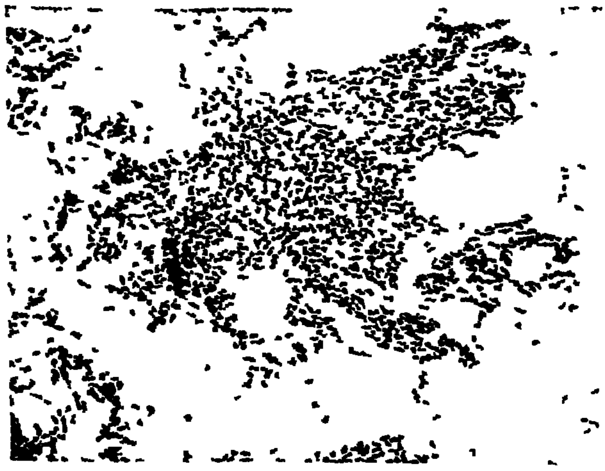

Fig 9—Case 4 nodule of mixed-dust fibrosis (Hæmatoxylin and eosin. ×32)

of nitrogen, but, on the other hand, they may have originated in early life, when he had pleurisy

Case 5—A man, aged 37, had been employed as an oxyacetylene cutter in an engineering works for six years He then did odd jobs for six years, followed by six years in the Army, and then a further three years' cutting He was examined by a mass miniature radiography unit about two months before his death, and " no significant change " was found in his film He committed suicide by hanging

Necropsy findings—Except for some general browniness, his lungs appeared normal to the naked eye Microscopically there were congestion and œdema, very little dust, and no fibrosis Chemical analysis gave, as percentages of the weight of dried lung, ash 1 95, total silica 0 06, free silica 0 03, iron (as ferric oxide) 0 54

Comment—No fibrosis was found in the lungs of a man employed for nine years as an oxyacetylene cutter

Discussion

It is generally believed that the inhalation of iron-oxide dust does not lead to fibrosis in the lungs or produce disability, but that the retained dust gives X-ray shadows that may be indistinguishable from fibrotic pneumoconiosis The condition is usually called " siderosis " (Doig 1949, McLaughlin 1950, 1951) Welders and oxyacetylene cutters commonly inhale iron-oxide fume, and not infrequently show shadows in X-ray films of their lungs However, few welders are exposed only to iron oxide some of them work in places such as the fettling-shop, where there is a mixed silica dust produced by other operations, most of them nowadays use rods coated with various materials, the metal which they work on may not be iron or may contain metals other than iron, and if they work in enclosed spaces, oxides of nitrogen and possibly other gases may irritate the respiratory tract

When one recalls how difficult it may be to ascertain what employment a man may have had during every part of a working life of forty or more years, and to imagine the conditions under which he may have worked many years before, it is evident that great caution must be used in interpreting the cause of any changes found in the lungs at necropsy This, however, does not apply when the only findings are siderosis with no fibrosis or only microscopic fibrosis In such cases one can say with confidence that iron-oxide dust has not produced any significant pathological lesion

So far as we have been able to ascertain, none of the 4 electric-arc welders described above had been exposed to any obvious risk from silica dust, but all had used coated electrodes, and case 4 had been exposed to fumes from burning paint Cases 1 and 4 showed very slight mixed-dust fibrosis with nodules that were just visible and palpable after twenty-nine and twenty-eight years' welding respectively, case 3 showed mixed-dust fibrosis of insignificant degree and only found microscopically after more than thirty years, and case 2 had no fibrosis after forty years' welding In none of them do we believe that mixed-dust fibrosis was responsible for death or produced any recognisable disability

The only oxyacetylene cutter showed slight accumulation of dust in his lungs and no fibrosis, but he had worked as a cutter for only nine years, with a twelve-year break between two periods of cutting

We consider that it is established beyond doubt that considerable quantities of pure iron oxide can be inhaled and remain deposited in the lung tissue without producing fibrosis Slight degrees of fibrosis may be present in the lungs of some electric-arc welders, we believe that this has not been caused by iron oxide but by other constituents of the welding fume, or possibly by some of the gases evolved In our experience the degree of fibrosis present, even in welders with long experience, has not been sufficient to cause any disability More severe degrees of fibrosis amounting to mixed-dust pneumoconiosis, associated in some cases with disability, have, in our experience, occurred only in welders exposed to extraneous sources of silica, such as that found in fettling-shops of foundries

Summary

Details are given of 4 electric-arc welders and 1 oxyacetylene cutter who came to necropsy These men had never worked in foundries or been exposed, so far as we could find out, to a silica-dust risk 2 of the welders showed very slight mixed-dust fibrosis in their lungs, 1 only microscopically visible fibrosis, and the 4th none The lungs of the cutter showed no fibrosis In those cases in which emphysema was present it was not usually of the focal type

Pure iron-oxide dust does not produce fibrosis of the lungs When fibrosis is found in the lungs of welders and others exposed to iron-oxide dust, it is probably due to other factors, including other substances inhaled with the iron oxide

We are indebted to Dr A H Cameron for the lungs of case 1, to Dr D M McClure for the necropsy report on, and for sections from, case 4, Mr R Conroy for the photomicrographs, and Dr J C McVittie, of the *Ministry of Pensions and National Insurance*, for the X-ray films of cases 1 and 4 and for help in many other ways

References at foot of next column

CONGENITAL CURLY TOES

AN INVESTIGATION INTO THE VALUE OF TREATMENT

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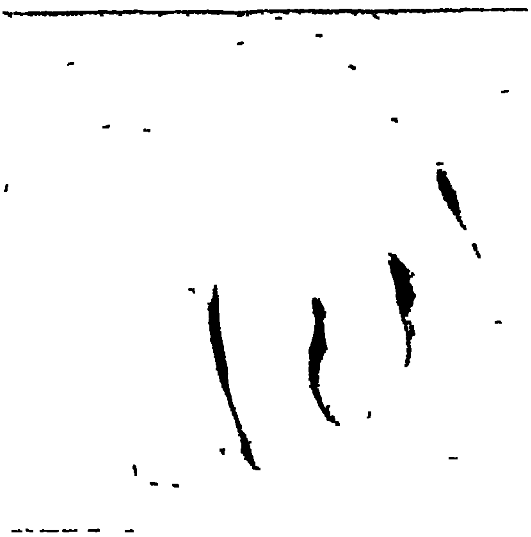
Deviation of one or more of the middle three toes is a common congenital abnormality The mother, anxious that her child should be normal in every way, seeks medical advice as soon as the deformity is noticed, and, according to whom she consults, she will be advised either that the toes will straighten themselves with growth or that some form of treatment is required The treatment usually advised consists of adhesive " over-and-under " strapping connecting the affected toe to its neighbours, in this way an attempt is made to hold the deformed toe in a corrected position

It was felt that this diversity of opinion concerning the value of, and even the necessity for, treatment warranted investigation, particularly since a thorough search of the literature revealed no account of the prognosis of this deformity either when left alone or treated This investigation is an attempt to remedy this deficiency

No consideration has been given to the common and well-documented condition of dorsal displacement of the little toe, in which the little toe overlies its neighbour, or to congenital hammer toe Both deformities have already received ample attention and are well described in standard textbooks—e g, Wiles (1955) The present investigation was concerned with congenital deviation of the third and fourth toes, more commonly the former, but occasionally



Congenital curly toes

also the second toe The toe is adducted and curled under its neighbour (see figure) The deformity is a mixture of adduction and flexion, mainly at the terminal joint, but also in the proximal, and is combined in the more severe cases with rotation of these joints, the nail coming to lie towards the lateral side Commonly two or even three toes are affected, and often both feet are involved

Trethowan (1925) described the condition in detail and believed that conservative treatment was successful "in the slighter and earlier degree of deformity" but emphasised that such treatment must be applied "with patience and assiduity" There has been no further contribution to this subject in the English literature since then

Investigation

The relatively trivial nature of the condition made follow-up of patients difficult, particularly because they had all been treated in infancy and could not be examined for the purpose of this inquiry until adolescence, the average age being 13

Fifty feet were available for examination (table I), the series is almost evenly divided between treated and untreated children

The treated children had all had the deformity held in attempted correction by means of over-and-under strapping for many months, the average being thirteen In only three children was this treatment started after the age of 2 years

TABLE I—COMPOSITION OF SERIES EXAMINED

No of children	Bilateral	Unilateral	Average age at follow-up (yr)	Average duration of treatment (mos)
29	21	8	13	13

TABLE II—RESULTS IN TREATED AND UNTREATED GROUPS

—	No of feet examined	No improved	No unchanged
Treated	21	5 (25%)	16 (75%)
Untreated	29	8 (27%)	21 (73%)
Total	50	13 (26%)	37 (74%)

When the children were examined in adolescence, the position of the toes was compared with the severity of the deformity when first seen, as recorded in the hospital notes If there was any doubt whether or not there had been improvement, the mother's opinion, if definite, was accepted Since this method of assessment was used in both the treated and the untreated children it does not detract from the validity of the results

Results and Conclusions

In no foot treated or untreated was any deterioration in the deformity found Growth of these crooked toes might have been expected to increase the apparent deformity, but this was not seen The number showing improvement, about 25% of the total, was almost evenly divided in proportion to the numbers in the treated and untreated groups (table II)

Eleven children (22%) had a known close relation similarly affected More detailed inquiry into this feature, together with examination of relations, would probably reveal a larger proportion The lack of symptoms in most cases would be unlikely to arouse attention among members of a family

None of the children examined had any symptom related to their curly toes, indeed the majority had forgotten that they had such an abnormality until the "follow-up" letter arrived

This inquiry has shown that over-and-under strapping has no significant effect on the outcome of this deformity of the toes However, since a quarter of the untreated cases improved and none of the remainder deteriorated, it is doubtful whether any form of treatment is worth while

The follow-up was not long enough to show whether symptoms occur in later life, that they did not do so by adolescence is no criterion However, from the relatively mild deformity and natural tendency for the toes of an adult to fit together by mutual pressure, it seems unlikely that troublesome symptoms would arise in many patients In fact, painful conditions of such curly toes are seldom seen in an orthopædic clinic, and, in any case, if they arise, the toe can be straightened by a simple operation in the outpatient department.

Undoubtedly many parents obtain satisfaction from knowing that something is being done to correct their child's "deformity" Perhaps this warrants recourse to treatment, but in most cases a simple explanation of the facts will save all concerned much time and valueless effort in treating a condition which requires no treatment.

DR HARDING REFERENCES

Barrie H J, Harding H E (1947) *Brit J industr Med* 4, 225
Britton J A., Walsh E L (1940) *J industr Hyg* 22, 125
Charr, R. (1955) *Amer Rev Tuberc* 71, 877
— (1956) *Ann. intern Med* 44 806
Doig, A. T (1949) *Edinb med J* 56, 230
— Duguid L. N (1951) The Health of Welders London
— McLaughlin A I G (1936) *Lancet* i, 771
— — (1948) *ibid* i, 789
d Onofrio, V, Passeri A (1950) *Rass Med industr* 19 276
Enzer N, Sander O A (1938) *J industr Hyg* 20 333
— Simonson E., Evans A M (1945) *ibid* 27, 147
Groh J A (1944) *Industr Med* 13, 598
Harding H E. (1945) *Brit J industr Med* 2, 32.
— (1948) *ibid* 5 70
— Glover S R. McLaughlin A. I G (1950) in Industrial Lung Diseases of Iron and Steel Foundry Workers (edited by A I G McLaughlin) London
— Grout, J L. A. Davies, T A. L. (1947) *Brit J industr Med* 4 223
McLaughlin A I G (1950) Industrial Lung Diseases of Iron and Steel Foundry Workers p 235 London
— (1951) *Brit J Tuberc* 45 105
—, Grout J L. A, Barrie H J Harding H E (1945) *Lancet*, i 337
— Harding H. E. (1956) *Arch industr Hlth* 14 350
Mann B T Lecutier, E. R. (1957) *Brit med J* ii 921
Poinso. R, Rouyer P Jouve G (1953) *Arch. Malad prof* 14 479
Sander O A (1944) *J industr Hyg* 26 79
Tebbens B D, Drinker P (1941) *ibid* 23 322
Thrvain, E Gerhardsson G, Forssman S (1952) *Arch industr Hyg* 6, 381
Wanek, H (1944) *Klin. Wschr* 23 67

Summary

An investigation into the value of treatment of congenital " curly toes " is described

The usual method of treatment with over-and-under strapping is both without effect and unnecessary

This investigation was undertaken at the suggestion of Mr G Lloyd-Roberts and it is a pleasure to acknowledge his kind help and advice and to thank him for allowing me to examine his patients I also wish to thank Mr R H Young for permission to examine children under his care at Victoria Hospital, Tite Street, and Miss B Kennedy, M C S P, for her generous help

REFERENCES

Trethowan, W H (1925) *Lancet*, i, 1257

Wiles, P (1955) Essentials of Orthopædics, p 280 London

AEROPHAGY OF EFFORT

A SYMPTOM OF CORONARY-ARTERY DISEASE

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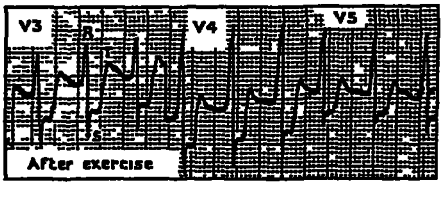
THE way to a man's heart is said to be via his stomach Symptoms often follow the same route Palpitation is frequently gastric in origin, angina of effort is often intensified immediately after a meal, flatulence is apt to follow the termination of an attack of paroxysmal tachycardia or indeed of anginal pain, and, finally, lesions of the œsophagus, and dysfunction of it, are known sometimes to simulate very closely the pain of myocardial infarction or of angina of effort

Berman (1957), in a paper entitled Dyspepsia of Effort, emphasises the relationship between exercise and gastric symptoms but does not specifically refer to aerophagy, although in three instances the dyspepsia overshadowed the anginal pain

The present case is a further gastrocardiac example of a type hitherto undescribed

A man, aged 65, began to have typical intermittent claudication in May, 1955 Previously he had been able to walk 8–10 miles a day without symptoms On clinical examination his cardiovascular system was normal except for a slightly raised diastolic blood-pressure (158/100 mm Hg) and some coolness of his legs and feet Electrocardiography showed a Q wave in leads III and VF The T wave was flat in lead III but normal in VF Deep inspiration diminished these abnormalities Radiologically the heart was normal in size and shape When he was seen in June, 1956, and again in July, 1957, his walking had improved He was otherwise symptomless The physical state and the electrocardiogram were unchanged

In August, 1957, he first noticed, and complained bitterly of, belching, accompanied by a feeling of tightness in his chest He associated the symptoms with walking and with excitement or emotion They would come on after he had walked about 50 yards and were absent at rest When he was examined in October, 1957, there was no change in his physical state, but he produced at intervals the noisy eruptive self-satisfying single belch of typical air-swallowing This recurred like an infrequent minute-gun during the examination A slight apical systolic murmur was now audible There was no other change in his resting clinical state or in the resting electrocardiogram An orthodiagram showed the heart to be a little larger His œsophagus and stomach were investigated radiologically by Dr George Simon and were found to be normal The patient was given a carminative mixture and advised about his method of eating The mechanism of his air-swallowing was also explained



S-T depression very well marked in leads V_3, V_4, and V_5, considerably more than could be accounted for by associated tachycardia

He was seen again on Nov 18, and this time the electrocardiogram was taken both before and after exercise Exercise produced depression of S-T from V_3 to V_5 (see figure) associated with much belching In view of the recent onset and the increasing severity of his symptoms he was treated by three weeks' rest in bed and was given a course of anticoagulant therapy He improved, but the symptoms persisted in a lesser degree

The psychological background is interesting During the first world war the patient went overseas and returned home with a functional visual disability He was unable to face the light, and a short spell of reading made him mentally confused He consulted several ophthalmologists both in this country and on the Continent Mr E H Cameron, of Edinburgh, reported on him on Nov 29, 1957, as follows

> " He has been coming to see me at intervals since 1944 and has always been difficult to deal with satisfactorily He had seen Dr A H H Sinclair here and the late Professor Ballantyne in Glasgow before coming to me, and told me that some years ago Dr Sinclair had told him he had ' optic neuritis ' I could never myself find any abnormality about his eyes, except a low refractive error and a low hyperphoria His corrected vision has always been 6/6 partly with each eye, and I have never been able to find any field changes His main complaint has been reading difficulty For this I could never find any evident cause and was forced to regard it as psychological "

The psychological factor seems to have been the link between the cardiac cause and the gastric manifestation

REFERENCE

Berman, B H (1957) *Circulation*, 16, 860

A SELF-COMPENSATING PNEUMATIC TOURNIQUET

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M B Cape Town
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From the Department of Anæsthesia, Groote Schuur Hospital, and the University of Cape Town

SURGERY of the limbs is greatly facilitated by the bloodless field which a tourniquet produces, this is often achieved by using the pneumatic cuff of a sphygmomanometer, particularly for surgery of the arm in adults and all the limbs of children The ordinary sphygmomanometer tends to leak from its connections and from the deflating valve, and must be watched constantly and attended to regularly if adequate pressure is to be maintained in the cuff

We have used the systems described herein and sketched in the diagrams and find that they keep a constant pressure in the cuff without any attention

The simpler system (fig 1) utilises an Adams reducing valve from an anæsthetic machine This valve ordinarily reduces the pressure in an oxygen or a nitrous-oxide cylinder to about 4–6 lb per square inch (which is equivalent to a pressure of 200–300 mm Hg) and can be set to various pressures within its working range by adjusting the tension of a spring seated against the diaphragm of the valve This adjustment is coarse, therefore, if it is used for inflating a tourniquet from a cylinder of medical gas, the pressure exerted by the tourniquet is not precisely controlled. However, the volume of gas used is limited to that required to inflate the cuff and to make good any leakage from the cuff and its connections.

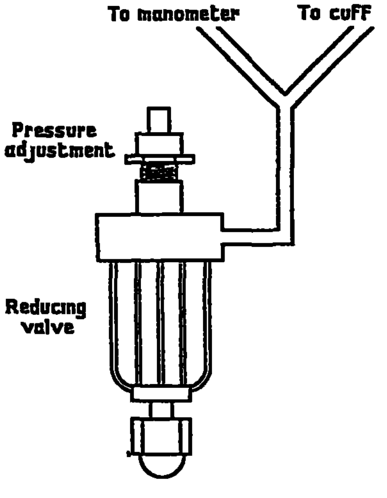


Fig 1—The simple system with coarse pressure control and low gas consumption

The more complex system (fig 2) also utilises a high-pressure gas and a reducing valve, but in this instance the valve is set to deliver greater pressures, say 8–10 lb per square inch (about 400/500 mm Hg), and there is a constant leak built into the system between the tourniquet and the control mechanism. A constant flow of gas is led from the reducing valve to the tourniquet, the volume flow being controlled by a needle valve on the low-pressure side of the reducing valve. By balancing this flow of fresh gas against the constant leak of gas, any desired pressure can be achieved in the tourniquet, and can be maintained as long as the source of gas lasts. The gas flows are small, but much more gas is used than in the simple system. However, the pressures in the cuff can be adjusted to within 1–2 mm Hg of the desired pressure.

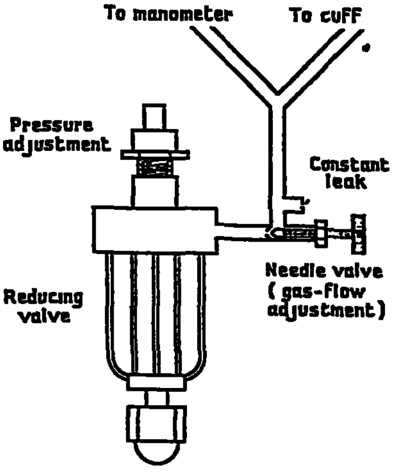


Fig 2—The more complicated system with fine pressure adjustment but larger gas consumption

It is advisable to use a mercury sphygmomanometer to monitor the pressures in the tourniquet, and, if the volume of mercury in the reservoir is adjusted, the manometer becomes a safety-valve as well as a measuring device, permitting gas to escape from the system if the pressure is raised to excess.

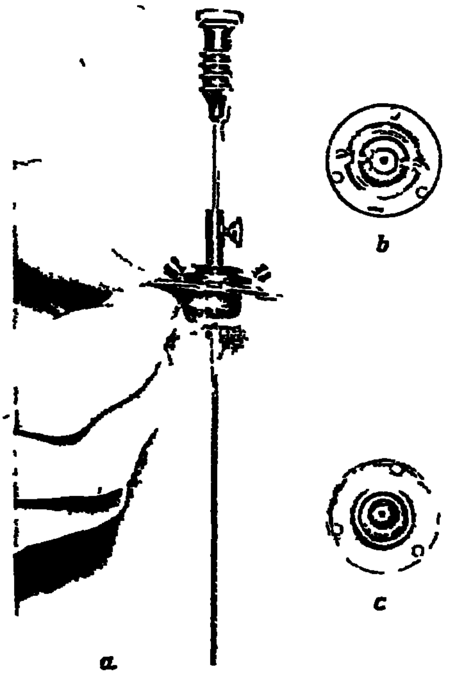
Both systems compensate for all but the grossest leaks. The constant leak also allows its system to compensate for increased pressures within the tourniquet—e g, from a constricting towel or bandage.

Our pilot model has been in satisfactory use for 6 months.

New Inventions

CUP-AND-BALL CHEMOPALLIDECTOMY APPARATUS

CHEMOPALLIDECTOMY and chemothalamectomy are now established procedures for the treatment of selected cases of parkinsonism and other hyperkinetic disorders. Most techniques in current use are complex, tedious and time-consuming. The cup-and-ball apparatus has been designed to simplify these procedures and to save time.



a Lateral view of the apparatus with the needle in place. *b* View from above. *c* View from below.

As with other methods, the target (globus pallidus or ventrolateral nucleus of the thalamus) is first located by means of pneumoencephalography. A burr-hole is then made, 13 cm from the nasion and 5 cm from the midline, and the cup-and-ball is fixed into the burr-hole with three pins which pass through the rim of the apparatus into holes drilled into the bone. A guarded drill of smaller size than the pin is used. A brain needle is passed a short distance into the brain through the hole in the ball in the approximate direction of the target (the ball can be fixed or moved by tightening or loosening the screws). Anteroposterior and lateral X-ray films are taken and any adjustments of the direction of the needle are estimated and carried out. The needle is then pushed inwards to the correct depth and the adjustable collar is fixed by means of the thumbscrew. The distance of the collar along the needle is measured for future checking. A small quantity of procaine is injected. If the point of the needle has reached the target, contralateral involuntary movement and rigidity should be relieved or greatly reduced. The scalp is then sutured except over the centre of the ball.

As the ball is fixed by screws, and the required depth of the needle is known, the needle may be removed and replaced on subsequent occasions for injection of absolute alcohol without further radiography. When the course of injections is finished the wound is opened, the apparatus removed, and the scalp resutured.

The apparatus is made by Lewis Bros London.

West End Hospital for
Neurology and Neurosurgery,
London, W 1

LESLIE OLIVER
M.B. Lond., F.R.C.S., F.A.C.S.

Reviews of Books

The Matrix of Medicine

Editor NICOLAS MALLESON, M D , M R C P , University College, London London Pitman Medical Publishing Co 1958 Pp 234 45s

THE theme of this book is the interplay of medical practice with the patterns of living in our community It seeks to explore some aspects of the social interfaces between the profession and the laity, whether the latter be the works foreman with a grouse or the anthropological studies of a nation It is a contemporary look around by sixteen different doctors peeping over the walls of their specialties, and meditating on what they see pass by In some respects it may be a ephemeral record, in some a renewed witness of eternal verities, for at the best it can be only a reflection of the outside world from the eyes of the sympathetic. It would be a mistake to think of medicine embedded in the social matrix in too concrete a metaphor, and the contributors emphasise the essential onward movement of the matrix and its aggregates, moving at irregular speeds and distances, more like moraines in a glacier, constantly altering each others' shapes and behaviour at the changing interfaces

It is in this way that each of the sixteen doctors looks across his own periphery General practice, public health, occupational health, hospital practice, and medical education, may all cherish their internal disciplines, but it is refreshing to see their exponents make a critical survey of their own impact upon the community This is a thought-provoking series of essays, to be dipped into at quiet moments, for most of us need to hear from time to time the whisper, *know thyself*

Intestinal Obstruction

CLAUDE E WELCH, M D , visiting surgeon, Massachusetts General Hospital, and clinical associate in surgery, Harvard Medical School Chicago Year Book Publications London Interscience Publications 1958 Pp 376 79s

IN this admirable book, Dr Welch has achieved the laudable aim of packing a small volume with information yet making it readable Its tone breeds confidence, for the chapters are studded with practical instructions which can come only from wide experience In the chapter on intubation for example, the author is not content with the usual information, for he also considers the complications everybody has encountered but seldom reads about knot formation, inability to withdraw the tube, rupture of the mercury-filled balloon are some of those mentioned It is refreshing too to read the categorical statement that it may be very difficult to place the tip of a Miller-Abbott tube in the pylorus There is a fine chapter on replacement therapy and a full bibliography The book will give excellent guidance at all stages of a surgical career, and it reflects great credit on the Massachusetts General Hospital

An Introduction to Psychopathology

D RUSSELL DAVIS, M A , M D , M R C P , D P M , reader in clinical psychology, University of Cambridge London Oxford University Press 1957 Pp 388 30s

As psychologist and psychiatrist, Dr Russell Davis is well equipped to write a book on this unsettled subject In a revealing passage in his opening chapter he gives due weight to clinical data as sources of evidence but suggests that many difficulties now besetting psychopathology are attributable to the emphasis, in contemporary British psychiatry, on somatic manifestations and constitutional causes of mental disorder This novel view seems at variance with the current dominance of psychoanalytic theory in psychopathology Dr Russell Davis depends not on the methods of psychoanalysis but on correlation and experimental procedures His exposition is lucid and informative, and ranges widely besides familiar themes, such as experimental neurosis and the effects of brain damage, he has chapters dealing with ecological factors, recent behaviour theories, and other biological aspects of psychopathology He adduces much evidence from the literature of the subject but does not examine it rigorously, nor do justice to the extensive German contributions he does not include Jaspers' unrivalled text in his list of about 300 references

Reflexogenic Areas of the Cardiovascular System

C HEYMANS, M D , professor of pharmacology, University of Ghent, E NEIL, M D , D SC , John Astor professor of physiology, University of London, Middlesex Hospital Medical School London J & A Churchill 1958 Pp 271 56s

THIS book is full of interesting and useful information for those who specialise in the study of the cardiovascular system and for laboratory workers concerned with the reactions of any organ, with the exception perhaps of those who study isolated tissues parted from the circulation The reflexogenic areas are not only concentrated in the carotid and aortic regions, similar sensory endings are distributed widely The reader is reminded too of the considerable activity of veins, both large and small, their supply of muscle may appear meagre, but the pressure against which the muscle must contract is low The importance of constriction of the veins probably lies in the modification of venous capacity, rather than in changes of resistance to flow

The first section of the book concerns the arterial baroreceptors, and the second the chemoreceptors, and each section begins with an account of the minute anatomy of the sensory areas A third section is devoted to the cardiopulmonary reflexes The subjects are discussed from every angle methods of study, general effects of stimulation, the local effects in organs of the general vascular response, the effects of anæsthetics and other drugs, and similar reflexes arising in parts other than the circulation.

It is clear that the chemoreceptor system has many facets of interest It is of direct importance in all considerations of respiratory control, whether in eupnœa, exercise, hypercapnia, or anoxia Thus this part of the book will appeal to the specialist in respiration, and so too will the third section

Although the baroreceptors directly affect the circulation and the chemoreceptors more directly concern respiration, one system cannot be affected without modification of the activity of the other and this mutual interdependence is discussed A small section is concerned with work on the still ill-understood volume receptors The last chapter is a miscellany of cardiovascular reflexes of uncertain origin

The condition of the circulation affects the responses of all organs, and the chances are that many workers not directly concerned will find here references or information useful to them, as well as judgment, sometimes sharp, of published work

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Blood Groups in Man (3rd ed Oxford *Blackwell Scientific Publications* 1958 Pp 377 42s)—The new edition of this now standard textbook by Dr R R Race and Miss Ruth Sanger is actually a few pages shorter than the 1954 edition The text and bibliography have been thoroughly revised and some chapters have been rearranged A new chapter deals with the blood-groups of twins There has been much progress in four years, and new sections are devoted, for example, to the phenotype A_3 and to the surprising amount of new work on the ABH antigens The authors keep to the CDE notation of the Rh blood-groups and do not think that E B Ford's new system of nomenclature can yet be applied in this field Wiener's corresponding symbols are collected in a table for those who wish to use them, and thus avoids repetition in the text Race and Sanger now think that "it looks as if we are nearing the end of the blood-group systems which can be detected by the tests in use up to now" New antibodies are being found to belong to one of the nine established systems Race and Sanger think this is a gloomy prospect, and from the geneticist's point of view they may be right, but the pathologist will surely be cheered by the prospect of some limit to his labours This third edition remains an indispensable survey of everything about blood-groups in man complications, the disturbance to the patient was insignificant and postoperative discomfort slight **Dohlman's**[18] œsophagoscope has a jaw-like slit in the distal end to fix the common wall, and acts as the second electrode while the diathermy forceps are used to perform the operation by stages Two to three interventions at about fortnightly intervals are usually sufficient to give lasting relief **Harrison**[13] obtained good results in his series of 17 patients and found the operation particularly useful in the elderly

In the majority of cases, by the time the patient is seen by the surgeon, the pouch has reached a considerable size and symptoms are pronounced Total one-stage resection of the sac with careful repair and antibiotic cover is usually regarded as the treatment of choice in reasonably fit patients There is a place for diathermy division of the septum between the diverticulum and the œsophagus, especially in the frail, ill, and elderly patient, but this should not be undertaken by the occasional œsophagoscopist, and it is no substitute for diverticulectomy, which obviates the necessity for repeated admissions and the risks (admittedly small) of infection, hæmorrhage, or malignancy supervening in the remaining pouch With modern surgical and anæsthetic methods, ever fewer patients are unsuitable for a single-stage excision of a pharyngeal pouch

Annotations

PROGRESS IN RESEARCH

From the many research studies which the Medical Research Council supports, some each year are selected for review in its annual report Each report thus contains a small collection of authoritative essays, which are readable and up to date and do not confine themselves to work done under the Council's auspices Because the essays could obviously be read with advantage and pleasure by a great many people—especially practising doctors—who would not normally buy the full report, the Council has once again had them reprinted, under the title of "Current Medical Research" This year's issue[1] covers the following fourteen topics

The Architecture of a Protein Molecule
The Development of Respirators[2]
Influenza in 1957
"New" Viruses of the Respiratory and Intestinal Tracts
Viral Interference and the Substance "Interferon"
The Changing Pattern of Serological Tests for Syphilis
The Spinal Cord in Poliomyelitis
Community Surveys in the Study of Rheumatoid Arthritis
The Mechanism of Fever
5-Hydroxytryptamine (HT)
Female Sex Hormones and their Quantitative Estimation
Experimental Studies on Radiostrontium
Experimental Leukæmia
Genetics of Eye Disease

More detailed and comprehensive information about the work now proceeding with the Council's help will be found in the report itself[3] In the year 1956–57, ended last September, its establishments consisted of the National Institute for Medical Research, the M R C laboratories in the Gambia, 44 research units, and 21 research groups, and it was also supporting research at cancer institutes From public funds in the financial year 1956–57 it spent £2,541,549 on ordinary account and £51,230 on non-recurrent account, compared with £2,325,430 and £76,226 in the previous year Of this money 19 6% was spent on the National Institute for Medical Research, 58 8% on research units, groups, and external staff, 7 8% on special grants, and 8 7% on temporary research grants and training awards The income from benefactions, which are gratefully acknowledged, was £115,785 For the financial year 1957–58 Parliament voted a grant-in-aid of £2,680,500, a supplementary grant-in-aid of £95,000 (necessitated by pay awards and other obligatory commitments arising during the year), and £37,500 on non-recurrent account The cost of the Public Health Laboratory Service, which is administered by the Council, is met separately by the Ministry of Health

The members of the Medical Research Council are

The Earl of Limerick (chairman), Sir Geoffrey Vickers (treasurer), Mr Richard Fort, M P, Sir George Pickering, F R C P, Prof Bradford Hill, Prof G F Marrian, Prof R C Garry, F R F P S, Mr H J Seddon, F R C S, Prof G Payling Wright, F R C P, Dr Denis Hill, Prof C H Stuart-Harris, F R C P, and Prof A A Miles, F R C P, with Sir Harold Himsworth, F R C P, as secretary

The Clinical Research Board consists of

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THE CHRONIC RESPIRATOR PATIENT

Of late years the treatment of patients with respiratory paralysis from whatever cause has progressed remarkably, and as a result patients with poliomyelitis have survived very severe attacks but have been left with permanent respiratory weakness The total number is not large, but it will increase each year until vaccination against poliomyelitis is available to those beyond adolescence, for it is in young and middle-aged adults that poliomyelitis is most severe and leaves most permanent damage Despite the relatively small number of these patients, they constitute an important clinical and administrative problem, for they make heavy demands on nursing and medical staff

Dooley[1] has reviewed the long-term care of patients who require artificial aid to respiration, basing his figures on a review in Britain in June, 1956 At the upper end of the scale are those who need assistance with respiration for part of the day or perhaps only at night, and Dooley records such a patient who was a house-physician in a London teaching hospital, travelling about the hospital in an electrically operated chair For this type of patient a cuirass or a breathing-jacket is excellent, the principal disadvantage being that some patients find them irremediably cold For the most severely paralysed—those who at best can breathe unassisted for a few minutes—the cuirass and the breathing-jacket are not suitable, and these patients are either nursed in a tank respirator or have a tracheotomy and are given artificial respiration by intermittent positive pressure In either case their spontaneous breathing may be much improved by glossopharyngeal ("frog") breathing Even if these patients have very little power in their limbs it is quite wrong to suppose that nothing can be done for them With suitable apparatus they can read, turning over the pages with an electric switch operated, if necessary, by the chin Electric typewriters are so light to operate that those with

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[1] Current Medical Research H M Stationery Office 1958 Pp 54 3s 6d Obtainable from H M S O, York House, Kingsway, London, W C 2, or through any bookseller
[2] This essay was reviewed in our leading article of Aug 9 p 305
[3] Report of M R C for year 1956–57 H M Stationery Office Cmd 453 13s

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[1] Dooley, D *Mon Bull Minist Hlth Lab Serv* 1958, 17, 124

very weak upper limbs can use them, and if even this is not possible they can be operated by a rod held in the mouth Quite ambitious pictures have been painted with a brush held in the mouth

Such patients can be treated at home provided that they can be supervised, and the ability to go about the outside world in general and home in particular provides a greater boost to their morale than anything else There are some differences of opinion on how this is best achieved Undoubtedly, if a patient has a tracheotomy in the acute stage it should be closed when he recovers enough power to breathe spontaneously for several hours a day But it is less certain whether tracheotomies should be closed in those who remain permanently with complete, or very severe, respiratory paralysis and can breathe spontaneously for only a few minutes One policy is to close the tracheotomy and treat the patient in a tank respirator, the advantage of this lies in the reduced risk of pulmonary infection The alternative is to maintain the tracheotomy, giving artificial respiration by intermittent positive pressure, the danger of pulmonary infection may be counterbalanced by the greater ease of treating this, since secretions can so readily be aspirated from the chest The question is still unresolved, but possibly the decisive factor will be mobility Although it is possible to travel extensively in a tank respirator it is by no means easy to do so, and air travel is virtually excluded With intermittent positive-pressure respiration, on the other hand, a respirator which has a 12-volt motor, such as the Radcliffe Respiration Pump, can be housed with an accumulator that will last 24 hours on a shelf attached to the back of a wheelchair This enables the patient not only to get about in the neighbourhood of his home or hospital, but even to visit places of entertainment The ease with which such patients can travel by air has been demonstrated when Britons who have contracted poliomyelitis in Africa or the Far East have been flown to England

When a patient with respiratory weakness leaves hospital it is essential that he should know where to turn for immediate help if he gets into difficulties of any kind In most parts of the country there is a service for bringing to hospital people with acute respiratory paralysis, and usually these teams are most suitable for giving assistance also to more chronic patients

TREATMENT OF RHEUMATOID ARTHRITIS WITH GOLD

THIRTY years after the first account of the use of gold salts in the treatment of rheumatoid arthritis [1] [2] their place is still not firmly established Several careful studies have provided weighty evidence that gold can induce a remission, but their conclusions have not been universally accepted, and the question is now being submitted to the test of a statistically controlled clinical trial in this country

Those who accept that gold is effective have to choose a course of treatment calculated to produce a good response with the minimum risk of toxic effects The commonly used homœopathic doses, unlikely either to influence the disease or to produce signs of toxicity, are clearly not the solution, and a report from Philadelphia[3] supports the belief that the dosage of gold salts should be tailored to the needs of the individual patient Starting from the premise that gold can induce a remission, but that some patients are more resistant to treatment than others, Smith et al [3] sought to explain differences in response by variations in the rate of excretion of gold in the urine Measurements of excretion led them to the conclusion that a predetermined dosage may fail to be effective because the patient excretes gold unduly rapidly, or may quickly lead to toxic effects if excretion is less than normal Differences in the duration of remission are due, they find, to the same causes Treatment must be designed to achieve an effective accumulation of gold in the body by giving a weekly dose which exceeds the amount excreted by the kidneys and by other routes Normally patients receiving weekly injections of 25 mg of gold secreted about a seventh of this amount in the succeeding week, one patient excreted 28% of each dose in the week after injection, and did not respond until the dose was raised to a point at which the excretion-rate amounted to only 14%

In routine practice it is not feasible to regulate the dosage of gold by measuring its excretion, and Smith et al suggest a method whereby the patient's response to treatment can be used as a guide After 12 weeks on a standard weekly dose, patients are divided into those showing some improvement and those whose condition is unchanged The former continue to receive the same weekly dose until they have been in remission for 1-2 weeks, and are then given a maintenance dose at longer intervals The unresponsive group proceed to a higher weekly dose, and to a second division at which the favourable reactors join the maintenance programme and the remainder move to a still higher dose Maintenance treatment is continued for an arbitrary period of 8 months When this method was used, 82% of patients had a remission, the corresponding figures for two types of standard course were 54% and 66% Smith et al hope that an even higher proportion of remissions will be achieved as refractory patients receive progressively more intensive treatment

Some years ago Lawrence[4] suggested a rather similar flexible dose scheme in which a fall in erythrocyte-sedimentation rate (or, better, in fibrinogen level) is used as a warning that the weekly dose of gold should be reduced This is consistent with the common observation that toxic reactions follow quickly on a good clinical response Lawrence held that the distribution of gold in the body was more important than its total concentration, believing that while the sedimentation-rate is high the skin and other potential sites for toxic effects are protected from high concentrations of gold by the readier diffusibility of the metal in areas of active inflammation and increased capillary permeability When the disease becomes less active this mechanism no longer operates and toxic reactions become more likely By adopting a flexible programme of dosage Lawrence reduced the incidence of stomatitis, and lesions of both mouth and skin became mild and transient rather than persistent and distressing disabilities Both Smith et al and Lawrence are prepared, in patients who have had toxic signs, to continue treatment with gold at a suitably adjusted dose level After mild toxic reactions had subsided Smith et al encountered subsequent undesirable reactions no more often than in patients treated with standard courses Severe toxic reactions often result from failure to interrupt treatment promptly when early signs develop

A flexible dosage programme may improve the results of treatment with gold, but it clearly calls for full appreciation of the principles involved, and for close supervision of patients and frequent measurements of sedimentation-rate Dermatitis and stomatitis, quickly detected, may by prompt adjustment of dosage be reduced to trivial complications, but more dangerous complications, such as thrombocytopenia, remind us that gold is a poison still to be handled with respect

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[1] Landé, K *Münch med Wschr* 1927, 74 1132

[2] Pick, E *Wien klin Wschr* 1927, 40, 1175

[3] Smith R T, Peak, W P, Kron, K M, Hermann, I F, DelToro, R A, Goldman, M *J Amer med Ass* 1958, 167, 1197

[4] Lawrence, J S *Ann rheum Dis* 1953, 12, 129

CANCER AND SOIL

MEN have long speculated whether differences in cancer incidence might not be due in some way to the soil As long ago as 1868, Farr and Haviland[1] examined the death-rate from cancer in England and Wales in relation to the geological map and concluded that the disease was commoner in low-lying clay areas liable to seasonal flooding by rivers, while more elevated districts, especially those with underlying chalk and limestone, tended to have low death-rates Haviland published several papers on the "medical geography" of Britain, with particular reference to cancer, the last of which appeared in 1899[2] Several observations by others indicated that the nature of the soil (using the term in its widest sense) influenced cancer mortality For the most part, these studies took the form of noting villages or small towns with a higher cancer incidence than neighbouring areas Behla[3] in Germany and Noel[4] in France concluded that cancer incidence was increased by insufficient drainage of the subsoil Williams[5] noted that in his country practice in Anglesey cancer was much commoner in a village where the soil was "heavy" than in a neighbouring village with a sandy subsoil or a third village standing on limestone, although the inhabitants of all three were similar in diet, occupation, and habits He deduced that "people living in clayey or retentive soils are more prone to cancer than those who dwell on porous soils such as sand or limestone"

These and other early reports have two serious weaknesses usually it was *total* cancer mortality that was studied, and allowance was not made for differences in the age-structure of the populations compared The study of regional variations in cancer incidence was put on a proper basis by Stocks,[6] who investigated the age-standardised mortality in England and Wales of cancer of separate sites Great contrasts were revealed One of the most striking concerned the mountainous areas of Wales, which seemed to show a mortality from stomach cancer three times as great as that of the chalk areas of south-east England Following the example set by Stocks, regional variations in cancer mortality have been studied in the Netherlands, where Tromp and Diehl[7] found that municipalities situated on peaty soils had a significantly higher mortality from stomach cancer than districts where sandy soils or river-clays predominated In a study of the incidence of cancer in Anglesey, Davies and Wynne-Griffith[8] found that stomach cancer tended to arise more commonly on those soils which show great biological activity because of an equable distribution of moisture at all seasons These soils would tend to have a high content of organic matter Legon[9] has compared the loss of weight on ignition (which, in the absence of calcareous matter, may be taken as an index of organic content) of samples of top soil from areas in North Wales and the Welsh Marches He found that this characteristic varied directly with the mortality from gastric cancer

Investigations into the relationship of soil to cancer of the stomach have now been carried a stage further In the course of field research covering North Wales and parts of Cheshire, Stocks[10] arranged for soil samples to be obtained from the gardens of the last residence of persons recently deceased from cancer The investigation covered the intestinal cancers as well as cancer of the breast and of the lung In addition, similar soil samples were taken from the residences of persons who had died from causes other than cancer, in order to provide a control series Some 1200 "cancer" soils and about 400 control samples were obtained The region chosen is of particular interest because the unusually high mortality from stomach cancer in North-West Wales (already referred to) is somewhat anomalous In England and Wales as a whole the disease has a substantially higher mortality in urban than in rural areas Accordingly a lower-than-average mortality might be expected in North-West Wales From the pattern of blood-groups, also, less gastric cancer than usual might be expected in this area, because here the proportion of group-A people is lower than average Racial predisposition can be discounted, because persons of Welsh extraction living outside Wales are not unduly susceptible to the disease The evidence therefore points to some local factor as being responsible for the excess mortality

The soil analyses reported hitherto[11] have revealed two interesting associations—though at this stage these must be regarded as tentative Garden soils from houses where a person has died of stomach cancer after fifteen or more years' residence have higher median concentrations of zinc and chromium than soils of similar gardens elsewhere in the same area where a person has died of a cause other than cancer or of cancer after residence of less than two years Cobalt, iron, lead, titanium, and vanadium showed no statistical association with cancer, while nickel, the other trace element which was examined, showed a negative association No explanation can be offered, but zinc is an essential element in the molecule of carbonic anhydrase enzyme and also possibly of the insulin molecule, and some early work suggests that zinc may be concerned with the glycolytic processes of tumour cells But the zinc-cancer association, being evident in areas outside North Wales as well as in the high-cancer area, though it may eventually prove to be in some way related to the general level of incidence, cannot be held to account for the excess mortality in the region

The association described by Davies and Wynne-Griffith may, on the other hand, prove to be the local factor which accounts for the excess, because in North Wales, but not elsewhere, the organic content of soil was related to gastric cancer but not to other cancers Three indices of organic content were used, and all gave broadly similar results Cancer of the stomach occurs more commonly in relation to soils with a high organic content after residence of ten to nineteen years and with moderately high content after residence of twenty years or more

This work on soils is being pursued at the Department of Agricultural Chemistry of the University College of North Wales, where arrangements have been made to analyse a common garden vegetable grown on "cancer" and "non-cancer" soils

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[1] Farr W, Haviland, A *Proc med Soc Lond* 1868, Nov 30
[2] Haviland, A *Practitioner* 1899 62, 416
[3] Behla R *Z Hyg.* 1899, 32, 123
[4] Noel, L Sur la topographie et la contagion du cancer Paris, 1897
[5] Williams W H. M D thesis, Edinburgh, 1914
[6] Stocks, P Regional and Local Differences in Cancer Death Rates H M Stationery Office, 1947
[7] Tromp, S W Diehl, J C *Brit J Cancer*, 1955 9 349
[8] Davies R I, Wynne-Griffith G *ibid* 1954, 8, 56
[9] Legon C D *Brit med J* 1952, ii, 700
[10] *See Brit med J* July 12, 1958, p 99
[11] Stocks, P British Empire Cancer Campaign annual report for 1957, supplement to part ii London, 1958

MIDDLE AGE IN NEW GUINEA

A CITIZEN of Great Britain, on reaching the age of 50, may find that since his student days his weight has gone up 15 lb, that his systolic and diastolic blood-pressures are now 25 and 10 mm Hg higher, and that the level of cholesterol in his serum has risen by 30 mg per 100 ml Such a man can certainly call himself normal and claim to represent the man-in-the-street, and, if he reads medical textbooks, he will have no difficulty in finding authorities who state that these rises are physiological—whatever that may mean

There have been several reports that such rises do not occur in some groups of men or women who lead a primitive life, for the most part unaffected by the Industrial Revolution Some of these are based on limited observations, but Whyte [1 2] has just completed a field study in which measurements were made on over 600 natives of New Guinea Good modern methods of measurement and of statistical analysis were used It was found that in both men and women in New Guinea systolic blood-pressure and serum-cholesterol are unchanged on reaching middle age, but that there is a fall in diastolic pressure of about 10 mm Hg and a fall in body-weight of about 10 lb

The natives of New Guinea are very small, the average height of the men being only 5 ft 1 in, but their weights were normal for their heights, judged by the Metropolitan Life Insurance Company standards They also appeared muscular and of good physique This suggests that genetical rather than dietary factors are mainly responsible for their small size The surveys were carried out in two districts—the highlands, where altitudes range from 5000 to 9000 feet, and on the coast In both the population is sparse and the small villages widely scattered Their diets contain little protein, the estimated intake being 30 g a day in the highlands and 40 g a day on the coast Both groups consume extremely little fat, and the highlanders also have little or no salt, which those on the plains do not lack The virtual absence of fat in the diet can probably explain the absence of a gain in weight and of a rise in serum-cholesterol as age advances There was no difference between the highlanders and those on the coast in blood-pressure levels, despite their different salt intake, and so this study lends no support to the claim that high blood-pressure is attributable to a high salt intake In New Guinea the people are certainly not exposed to the "stresses and strains" of modern civilisation Whyte does not discuss their manner of living, but life is seldom easy in a primitive society and no doubt they have their worries and their emotional disturbances

In Great Britain the increases in middle age of weight, blood-pressure, and serum-cholesterol, described above as normal, are certainly compatible with health and a long life But larger increases are also common, and these are certainly associated with degenerative diseases of the heart and arteries From these diseases the natives of New Guinea seem to be singularly free Price, who has done 600 necropsies, informed Whyte that in only 1 case was death attributable to coronary-artery disease, and he found that atheroma was generally absent or very slight Hypertension is virtually absent among these people As Whyte remarks, the inhabitants of New Guinea lack many things—protein, fat, gross obesity, and city bustle Probably for these reasons they seldom suffer from degenerative cardiovascular diseases, yet they also lack the comforts and amenities of civilised life and the skills and energy necessary to protect themselves against infectious diseases To acquire these advantages man may need a lot of protein, fat, and city bustle Perhaps we cannot have it both ways

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[1] Whyte H M *Aust Ann Med* 1958, 7 36

[2] de Wolfe, M S, Whyte, H M *ibid* p 47

PLEURAL BIOPSY

A DIAGNOSIS of tuberculous pleural effusion commits the patient to protracted chemotherapy and sets administrative wheels in motion, hence it is highly desirable to confirm this diagnosis But since, even with the best bacteriological technique, tubercle bacilli can be grown from the pleural fluid in only some cases, pleural biopsy has been used to obtain additional information, [1–10] and Hill et al [11] and Weiss [12] now report on the value of this increasingly popular procedure

In 23 cases of presumptive tuberculous pleural effusion without demonstrable pulmonary disease, Hill et al cultured tubercle bacilli from the fluid in only 4 cases, whereas investigation of biopsy material led to a diagnosis in 15 cases In 5 of these 15 cases the diagnosis was based on the histological appearances alone, in 9 histological evidence was confirmed by culture of the tubercle bacillus, and in 1 the diagnosis was made on culture results alone In a further 9 cases, in which there was pulmonary as well as pleural disease, biopsy was of no help, the diagnosis was established by other means in 7 cases, and pleural biopsy was merely confirmatory in 4 of these

Weiss carried out pleural biopsy in 31 cases of presumptive tuberculous pleural effusion with or without pulmonary involvement, and made a histological diagnosis of tuberculosis in 23 Pleural fluid was cultured in 27 of the 31 cases and was positive in 16 instances, and the combined results of pleural biopsy and culture of the fluid gave positive findings in 27 of the 31 cases Hill et al warn that the finding of a non-specific pattern of pleural inflammation does not exclude tuberculosis, and these workers and Weiss agree that, although pleural biopsy may occasionally demonstrate a malignant pleural condition, the procedure is of value chiefly in establishing the presence of tuberculosis, as in this condition the pleura is usually very extensively involved

Pleural biopsy may be carried out as an open operation under general or local anæsthesia, or blindly using a special needle such as a Vim-Silverman Despite the necessity for a surgeon and an operating-theatre, Hill et al prefer open operation under local anæsthesia to needle biopsy, because a suitable piece of pleura can be selected and enough removed to permit bacteriological as well as histological examination Weiss, on the other hand, maintains that if thoracentesis is performed needle biopsy may as well be done at the same time and open operation kept in reserve—a reasonable opinion in view of his high proportion of successes with the simpler method

Prof CHEVALIER JACKSON, pioneer of œsophagoscopy and bronchoscopy, died in Philadelphia on Aug 16 at the age of 92

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[1] Sutcliff, W D, Hughes, F, Rice, M L *Dis Chest*, 1954, 26 551

[2] Small, M J, Landman, M *J Amer med Ass* 1955 158, 907

[3] Stead, W W, Eichenholz A, Stauss, H K *Amer Rev Tuberc* 1955, 71, 473

[4] De Francis N, Klosk, E, Albano E *New Engl J Med* 1955, 252, 948

[5] Heller P, Kellow, W F, Chomet, B *ibid* 1956, 255, 681

[6] Breckler, I A, Hoffman, M C, Hill, H E, Hensler, N M, Hukill, P B *ibid* p 690

[7] Douglas, B E, Carr, D T, Bernatz, P E *Amer Rev Tuberc* 1956, 74, 954

[8] Donohoe, R F, Katz, S Matthews, M J *Amer J Med* 1957, 22, 683

[9] Mestitz, P, Pollard, A C Purves M J *Lancet*, 1957, ii, 873

[10] Weiss, W *Amer J med Sci* 1957, 234, 431

[11] Hill, H E, Hensler, N M, Breckler, I A *Amer Rev Tuberc* 1958, 78, 8

[12] Weiss W *ibid* p 17

Occasional Survey

EXERCISE-TOLERANCE TESTS

E. A. Harris
M.B. Lpool, Ph.D. Edin., M.R.C.P.

Impairment of the capacity for physical exertion is a common symptom of disease. In cardiopulmonary disease it is by the severity of this symptom and its rate of progression or regression that the necessity for treatment, the type of treatment, and the response to treatment are largely judged. Assessment of the degree of impairment at any given time is usually made on the basis of the clinical history, but, valuable though the latter may be, it can never be objective, since it is influenced by the motives, personality, and intelligence of both patient and physician. The lack of objectivity is particularly regrettable when decisions for or against surgical measures such as mitral valvotomy are in the balance. In many such cases help can be obtained from cardiac catheterisation, but this is a routine procedure in only a few centres, and in any case it cannot be said to assess the patient's capacity for any ordinary activity. A reliable, simple, repeatable, and safe "exercise-tolerance test" would therefore be very useful. Despite the attention given to this question by many investigators the ideal test has not yet been realised.

Clinical exercise-tolerance tests are closely related to tests of fitness for athletic, industrial, and military purposes. In this article existing tests in all these fields are briefly surveyed. The emphasis throughout is upon tests which are relatively simply performed and therefore technically suitable for routine application. The tests so far proposed fall into three groups: (1) those based on ventilatory measurements; (2) those based on records of heart-rate; (3) those involving measurements of maximum oxygen consumption or oxygen debt.

VENTILATORY MEASUREMENTS

The Ventilatory Equivalent

When the ventilation-rate increases abnormally on exercise, as in many types of cardiac and pulmonary disease, the ratio of ventilation to oxygen uptake or to carbon-dioxide output is abnormally high. These fractions were termed the "ventilatory equivalents" (V.E.) for oxygen[1 2] and for carbon-dioxide.[3] They were originally regarded[4 5] as reflecting alterations in pulmonary blood-flow, and this view found a measure of acceptance.[6] However, the V.E. may be increased by nervous hyperventilation, by excessive ventilation of the dead space due to rapid shallow breathing,[7] and by the respiratory stimulus of metabolic acidosis, as in the lactic-acidæmia of exercise. Donald et al.,[8] for example, found no consistent relation between V.E. and pulmonary blood-flow during exercise in patients with mitral stenosis. The V.E. can be regarded as a rough index of ventilatory efficiency, but in the absence of other data it cannot be interpreted precisely.

The Respiratory Frequency

Wahlund[9] used the respiratory frequency as an index of working capacity, which he defined in this connection as the rate of work at which the frequency reaches 30 breaths per minute. This value was arbitrarily chosen as the limit of efficient respiration. Respiratory frequency is, however, a very variable function; it can be regulated consciously by the subject and is apt to be influenced by breathing apparatus in subjects unaccustomed to wearing it. Matthews[10] found the respiratory frequency to be useless as an index of exercise ability in patients with mitral stenosis.

The Hugh-Jones Test

Hugh-Jones[11] found that the ventilatory "debt" after 5 minutes' standard exercise was equal to the ventilatory "deficit" of early exercise in healthy people and in patients with emphysema who could finish the exercise. In patients who were unable to complete 5 minutes' exercise the debt exceeded the deficit and the difference was roughly proportional to disability. Stock and Kennedy[12] obtained similar results in mitral stenosis. In exercise below the healthy or emphysematous subject's aerobic capacity the debt never materially exceeds the deficit[13] and the exercise must be severe (for the particular subject) before the test begins to be "positive". It is thus a maximal test and as such may be undesirable in some conditions, though doubtless safe in emphysema. Its interpretation is also subject to the uncertainties surrounding the ventilation equivalent.

Comments

The current view of dyspnœa[14] is that it arises whenever ventilatory demand approaches the available ventilatory capacity. By measuring both of these, it should theoretically be possible to "measure" dyspnœa. The Hugh-Jones test depends partly upon ventilatory demand and supply during exercise. However, the observed ventilation during an exercise test may not be the true ventilatory demand for that rate of work, because the subject's unfamiliarity with the conditions of the test may induce unnatural breathing—usually hyperventilation but occasionally the opposite. Further, the potential candidate for industrial compensation may have a powerful motive for making himself appear as disabled as possible. Measurements of maximum ventilatory capacity too are subject to the patient's voluntary control; the resting value, moreover, does not necessarily apply to exercise. For these reasons ventilatory measurements have serious limitations when used alone as indices of performance.

HEART-RATE

The Recovery Heart-rate

(*a*) *Master's step test*[15 16] depends entirely on a single pulse-count taken sitting 2 minutes after standard exercise. Master asserted that the test would distinguish differences in disability which were otherwise undetectable. The grounds for this assertion are not clear.

(*b*) *The Harvard step test*[17] has been widely used in the athletic field and a more severe form of it (the "pack test") for military purposes. Since the recovery heart-rate curve is approximately exponential, it can be characterised if three points on it are known. The Harvard test utilises pulse-counts at 1–1½, 2–2½, and 4–4½ minutes of recovery, and these are incorporated into an index of fitness.

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1. Anthony, A. J. *Dtsch. Arch. klin. Med.* 1930, 167, 129.
2. Knipping, H. W., Moncrieff, A. *Quart. J. Med.* 1932, 25, 17.
3. Marais, O. A. S., McMichael, J. *Lancet*, 1937, ii, 437.
4. Simonson, E., Gollwitzer-Meier, K. *Z. ges. exp. Med.* 1930, 73, 330.
5. McMichael, J. *Clin. Sci.* 1939, 4, 19.
6. Levy, R. L. Disorders of the Heart and Circulation. London, 1951.
7. Elsasch, H. *Scand. J. clin. Lab. Invest.* 1952, suppl. 4.
8. Donald, K. W., Bishop, J. M., Wade, O. L. *J. clin. Invest.* 1954, 33, 1146.
9. Wahlund, H. *Acta med. scand.* 1948, suppl. 215.
10. Matthews, M. B. M.D. thesis, Cambridge University, 1954.
11. Hugh-Jones, P. *Brit. med. J.* 1952, i, 65.
12. Stock, J. P. P., Kennedy, M. C. S. *Lancet*, 1953, ii, 5.
13. Harris, E. A. Ph.D. thesis, Edinburgh University, 1957.
14. Donald, K. W. *Brit. med. J.* 1953, i, 415, 473.
15. Master, A. M. *Amer. Heart J.* 1935, 10, 495.
16. Master, A. M., Oppenheimer, E. T. *Amer. J. med. Sci.* 1929, 177, 223.
17. Johnson, R. E., Brouha, L. *Rev. canad. Biol.* 1942, 1, 171.

Master's test has not been critically re-evaluated, but criticisms of the Harvard test should apply more forcefully to Master's Cureton et al [18] compared the Harvard step test with the ability to perform a variety of gymnastic and athletic feats Their very thorough study showed a strikingly low correlation Taylor [19] concluded that the recovery heart-rate curve is not closely related to the capacity for exercise "It seems clear", he writes, "that one must look to the responses *during* exercise for critical measures of fitness for hard work" In the clinical field, Baldwin et al [20] found that in pulmonary disease there was no relation between pulse-counts, taken during recovery from exercise, and disability The causes of the raised pulse-rate after exercise are poorly understood and are probably related as much to peripheral vascular conditions, muscle tone, and posture as to cardiopulmonary status

The Heart-rate during Exercise

The measurement of heart-rate during exercise is technically more difficult than its measurement in the recovery period, but recent developments in instrumentation [21 22] have solved most of the technical problems Three tests have been proposed which make use of the heart-rate during exercise

(*a*) *Wahlund's test* [9]—The heart-rate, during the 3rd to 6th minutes of each of a number of exercises of different intensities, is counted and the heart-rate is plotted against the rate of work The rate of work corresponding to a heart-rate of 170 beats per min is taken as the "working capacity" To avoid error from extrapolation the exercise must be pushed to somewhere near the "working capacity", and this is therefore a *near-maximal* test Wahlund showed clear differences between dissimilar groups of healthy subjects and patients, but the value of the test in the individual subject is hard to assess from Wahlund's data

(*b*) *Astrand and Ryhming*,[23] having found that the heart-rate in the steady state of submaximal exercise could be correlated with the maximum attainable oxygen uptake ("aerobic capacity"), constructed a nomogram from which the aerobic capacity can be read if the work-rate (or oxygen uptake) and heart-rate are determined for a single submaximal exercise These workers suggested a clinical application for the test because it is a submaximal one There appears to be only a fair correlation between determined submaximal heart-rate and determined aerobic capacity, and there is much individual scatter in the published figures

(*c*) *Müller* [24] proposed what he termed the "*Leistungspulsindex*" (L P I), which consists essentially of the rate of rise of heart-rate with increasing rate of work The absolute heart-rate reached at any exercise level is not taken into account in calculating the L P I Muller showed fairly good correlation between L P I and an estimate of maximum performance and also demonstrated improvement in the index during a training programme in two subjects

It has been known for many years that "fit" subjects tend to have lower heart-rates than "unfit" subjects at the same rate of work, and also that patients with cardiac, pulmonary, and other disease respond to effort with a greater tachycardia than healthy people The factors responsible for the tachycardia of exercise are, however, poorly defined and are therefore difficult to control experimentally Consequently random fluctuations in these factors, while mutually compensatory when groups of subjects are compared, make individual comparisons unpredictable There is probably more chance of error from this source when the absolute heart-rate is the criterion, as in the Wahlund and Astrand-Ryhming tests, than when Muller's L P I is used For example, an athlete showed day-to-day variations in the first two of these tests of up to 20%, whereas his L P I remained almost constant [13]

All these tests utilising heart-rate during exercise have been introduced during the last 10 years and none has yet been critically reinvestigated *Muller's test appears*, a priori, to have advantages over the other two, but has never been assessed clinically Perhaps the heart-rate tests may yet be put on a more rational basis as more is discovered about the mechanisms of the tachycardia of exercise The findings of Harris and Porter,[25] for instance, indicate that the "heart-beat deficit" of early exercise might be developed as a possible index of performance, since it appears to parallel the oxygen debt At present, however, no exercise-tolerance test based on heart-rate can be confidently recommended for clinical use

MAXIMUM OXYGEN UPTAKE AND OXYGEN DEBT

Maximum Oxygen Uptake

This is the ultimate measure of the capacity of the oxygen transport and utilisation systems, and has been so recognised since the classical work of A V Hill and his school The maximum oxygen uptake is different for different types of exercise and is also increased by preliminary "warming up" [26 27] Taylor et al [27] have proposed it as an index of cardiorespiratory performance, and for healthy subjects it is probably the best index available Maximum oxygen uptake in exercise involving a large muscle mass is mainly limited, in health, by the maximum cardiac output [28] Since the measurement of maximum oxygen uptake involves maximum effort it is unsuitable for clinical purposes

Oxygen Debt

Margaria et al [29] found that the oxygen debt after standard treadmill exercise increased in rectilinear fashion with increasing exercise up to an oxygen uptake of about 2000 ml per min in a healthy subject At rates of work above this intensity the debt curve rose more and more steeply, becoming almost vertical at the limit of tolerance The end of the linear phase corresponded to the exercise intensity above which lactate began to accumulate substantially in the circulating blood In exercise at the same submaximal level the blood-lactate,[30] and the oxygen debt after exercise, are greater in the unfit subject The same was shown to apply in disease of the heart and lungs by Katz et al [31] and Nylin [32 33] These workers devised clinical exercise-tolerance tests based on this finding

Since significant differences in oxygen debt between

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18 Cureton, T K, Huffman, W J, Welser, L, Kireilis, R W, Latham, D E Endurance of Young Men Monographs of the Society for Research in Child Development, no 10 1945

19 Taylor, C *Amer J Physiol* 1944, 142, 200

20 Baldwin, E de F, Cournand, A, Richards, D W *Medicine (Baltimore)*, 1948 27 243

21 Austin, W T S, Harris, E A *Quart J exp Physiol* 1957, 42, 126

22 *Lancet*, 1958, i, 956

23 Astrand, P-O, Ryhming, I *J appl Physiol* 1954, 7, 218

24 Müller, E A *Arbeitsphysiologie*, 1950, 14, 271

25 Harris, E A, Porter, B B *Quart J exp Physiol* 1958, 43, 313

26 Furusawa, K *Proc roy Soc B*, 1926, 99, 155

27 Taylor, H L, Buskirk, E, Henschel, A *J appl Physiol* 1955, 8, 73

28 Mitchell, J H, Sproule, B J, Chapman, C B *J clin Invest* 1958, 37, 538

29 Margaria, R, Edwards, H T, Dill, D B *Amer J Physiol* 1933, 106, 689

30 Robinson, S, Harmon, P M *ibid* 1941, 132, 757

31 Katz L N, Soskin S, Schutz, W J, Ackerman, W, Plant, J L *Arch intern Med* 1934, 53, 710

32 Nylin, G *Acta med scand* 1933, suppl 52, p 1

33 Nylin, G *ibid* 1938, suppl 93, p 1

subjects may be found at exercise intensities well below maximum levels, tests based on debt measurements are suitable for clinical use. Moreover, it would seem almost impossible for a subject voluntarily to influence his oxygen debt, and this consequently provides a truly objective measure of performance Of all existing tests, this is the one which, from the clinical point of view, would probably most repay further study and development.

COMBINED TESTS

Composite indices have been proposed from time to time. Bruce et al [34] developed a "physical fitness index" (P F I) combining recovery heart-rate with ventilation equivalent While they thought this index helpful in the assessment of cardiac patients for operation,[35] it seems doubtful whether the P F I is fundamentally more reliable than its individual components

DISCUSSION

The term "exercise tolerance" is often used in clinical discussions, but few attempts have ever been made to define it. Wahlund [9] used it to mean the highest exercise intensity which the subject could maintain efficiently in a steady state But how do we recognise efficiency or inefficiency? The physiological responses to exercise, for the most part, follow a continuous gradation from the mildest exercise to the most severe, and at no point is it easy to say that exercise has become "inefficient" Wahlund was, as we have seen, obliged to use quite arbitrary levels of heart-rate and respiratory frequency as his criteria Alternatively we might, with Cureton et al.[18] and Taylor,[19] regard the subject's maximum performance as the only reliable criterion of his "exercise tolerance" In clinical work this definition is unhelpful (1) because of the risk involved in maximal exercise (one patient, at least, with mitral-valve disease, has died after exercise on a treadmill [34]), and (2) because one can never be sure of a patient's full cooperation and maximum effort A submaximal test is needed, but submaximal tests based on measurements other than oxygen debt have the disadvantage that there is no standard against which to assess them in clinical work—except for the history (and if this were reliable and quantitative there would be no need for an objective test) On the other hand an assessment based on oxygen debt has a physiological validity which requires no comparison with other and possibly spurious criteria The oxygen debt, indeed, is almost the only indication we have that the exercise which preceded it was "inefficient"

The oxygen debt depends upon the adequacy of the oxygen supply to the working muscles during exercise, and is thus influenced by the oxygenation of blood in the lungs, the oxygen-carrying capacity of the blood, the cardiac output, and the state of the arteries supplying the muscles These cover most of the causes of impaired working capacity It is nevertheless conceivable that a person with, for instance, mitral stenosis or hypertensive heart-disease may be forced to stop exercise owing to dyspnœa from pulmonary engorgement while the oxygen supply to his working muscles is still sufficient to avoid a lactacid oxygen debt If this is so, a test based upon oxygen debt might fail to reveal his true disability The limitation of exercise tolerance due to angina of effort also falls into a special category

From this brief survey it is clear that no clinical test of exercise tolerance has yet been developed to the point of practical usefulness In clinical tests a compromise usually has to be found between reliability and technical simplicity. The latter must, however, be evaluated in the context of current trends, and in view of the increasing refinement, complexity, and costliness of modern methods of diagnosis and treatment it would be unrealistic not to accept a reasonable degree of technical difficulty provided the test were reliable

The time has come to take stock of the advances in our knowledge of exercise physiology and pathophysiology and to see whether a reliable exercise-tolerance test can be devised The problems to be faced are, in detail, numerous, but the main lines on which further work might most profitably proceed are fairly clear Firstly, a good deal remains to be learnt about the precise conditions under which an oxygen debt is contracted and repaid in health and disease Secondly, a better understanding of the mechanisms whereby the heart-rate increases during exercise would remove much of the empiricism which surrounds existing tests based on heart-rate, and might point the way to a rational and reliable use of cardiotachometry for the assessment of exercise capacity

Meanwhile, can anything be done to supplement the patient's own account of his disability? The practice of walking upstairs or round the hospital grounds with the patient (or sending the house-physician with him!), besides requiring no apparatus and helping to keep the doctor fit, is often surprisingly informative It is not uncommon for the patient to score quite heavily in such a competition, and one then has little doubt that his exercise tolerance is reasonably good. The opposite result, in which the patient fares badly, must of course be interpreted with due caution.

SUMMARY

Existing tests of capacity for exercise are reviewed and their merits considered So far as the clinical assessment of exercise tolerance is concerned there is at present no suitable test of proven reliability The measurement of oxygen debt after standard exercise appears to be the most promising basis for such a test, but it probably cannot supersede measurements of pulmonary ventilation and heart-rate While the interpretation and limitations of ventilatory data are now well appreciated, more needs to be learnt about the tachycardia of exercise before tests depending on measurements of heart-rate can be put on a rational basis

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[34] Bruce, R A., Lovejoy F W, Yu, P N G, McDowall M. E. *Arch industr Hyg* 1951, 4, 236

[35] Bruce R A, Merendino K. A., Pampush, J J, Bergy, G G, Brock, L. L. *Amer J Med* 1956, 20, 745

Medicine and the Law

A Danger on the Roads

A Chester court was told on Aug 8 that heavy smoking may cause a driver to confuse the colour of traffic signals [1]

The defendant, who had driven across a road when the traffic lights were against him, and collided with a cyclist, told the police that he believed the signal was green and in his favour Through his solicitor he said he would not drive again until a specialist—who had diagnosed the condition of "smoker's eye —said he was cured.

Tobacco amblyopia, as a clinical manifestation of vitamin B_{12} deficiency, was discussed in our issue of Aug 9 [2]

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[1] *Daily Herald*, Aug 9, 1958

[2] Heaton, J M., McCormick, A. J A., Freeman, A. G *Lancet*, Aug 9, 1958, p 286.

Special Articles

STARTING A SCHIZOPHRENIC UNIT

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In June, 1957, we opened a schizophrenic unit for men up to about 35 years of age In it were gathered together 24 long-stay patients who had been scattered through the various chronic wards, together with 6 acutely ill schizophrenics under insulin treatment from the admission ward Our purpose was to de-institutionalise the long-stay patient, to prevent the acutely ill from becoming " chronics ", and to help both to fit themselves for return to the community wherever possible For those whose discharge did not ultimately prove practicable we hoped to make life happier and to prevent further withdrawal Our aims were (1) to reproduce real-life pressures by being no more, and little less, permissive than real life itself, (2) to bring the families into the treatment situation, and (3) to have maximum communication between patients, staff, and relatives

Social training of the chronic mental patient tends to veer between rigid habit-training and unlimited permissiveness Since our objective is always reintegration into the outside community, at however humble a level, we have taken pains to avoid both extremes Rigid habit-training leads to disappointingly little useful conditioning for independent activity, and unlimited permissiveness seems to require greater ego strength than the average schizophrenic possesses We have tried to be no more permissive than real life itself, but we also give as much opportunity for free choice and decision-taking as is possible This means that we do not leave the decision about working to the patient, any more than it is left to the ordinary person For nearly every adult male, going to work regularly is one of the unavoidable pressures of daily life, and this pressure is introduced into our unit to help the schizophrenic prepare himself for leaving the hospital Leisure, on the other hand, is relatively unorganised in normal life

In the average chronic ward, the position is the reverse of the real-life situation Entertainments are often laid on fairly lavishly and can be hard to evade, but work (though encouraged) is optional In our unit work is the one really compulsory thing No entertainments are available other than those organised by the patients, and, within very wide limits, the patients run the ward democratically

We lay great stress on the work always being on a community project of a finite nature, with something completed and concrete as an end-product, so that the patients can take pride in seeing a job completed, and can learn to work together as members of a team This develops group feeling and makes it possible to involve the very withdrawn in social and productive activity, since even the little they do is done in association with others (who tend to spur them on) and is a positive contribution

A vital step in returning the schizophrenic to the community is to help his family to accept him and to understand him, this means making a complete assessment of his social background and involving his relatives in the treatment We therefore have very full communication with the relatives, both individually and collectively, invite them to join in ward activities, and encourage them to have the patients home for weekends and holidays The families of many chronic schizophrenics often have very severe emotional difficulties and may either reject the patient outright or smother him with ambivalent solicitude, and helping them may have a decisive effect on the patient's recovery

We have full discussion with the patients at weekly ward meetings as well as individually, so that wherever possible they plan their own lives and understand the purpose and method of treatment The nurses and doctors meet weekly for full and frank discussion of plans, activities, and problems The psychologist, psychiatric social workers, and occupational therapists are invited to attend these meetings

Preliminary Planning

Our first tasks were to select the patients, find a ward for them, staff it, find suitable jobs for the work projects, and get adequate psychological and social information

We fixed an arbitrary upper age-limit of 35, and all the chronic patients of this age or under were interviewed by one of us All the departments were visited as possible sources of work, and the problem of finding a finite constructive job on which 20–30 men could work together was discussed with the head occupational therapist, administrators, engineers, gardeners, and indeed everybody we met

Full social and psychological assessment was planned with the psychiatric social workers and the clinical psychologist

Finally, the staffing was planned at a meeting of the physician superintendent with all concerned Despite the shortage it was considered vital to have a full complement of nurses, who should change as little as possible, to ensure continuity They originally consisted of a charge nurse, two staff nurses, and a student nurse on each of the two shifts Eventually, however, we had to give up the second staff nurse and have instead a nurse on duty from 7 A M to 5 P M

The ward selected was in the main hospital, so to go there was an apparently retrograde step for patients comfortably and " permanently " settled in modern " chronic " villas surrounded by pleasant gardens

24 long-stay patients were chosen, the criterion being a certain minimum capacity for communication, comprehension, and cooperation The standards were set deliberately low so that hallucinations, delusions, and a considerable degree of withdrawal did not disqualify The habitually disturbed, the incontinent, and the lost were, however, excluded 16 were voluntary and 8 certified The average number of admissions was 3 2, and the number of years since first admission varied from 1 to 16, the average being 6 5 21 patients had had insulin-shock therapy at some time, 18 electroconvulsion therapy, and 4 standard leucotomies Before transfer to the new unit 14 did some sort of hospital utility work, 5 did regular occupational therapy, and 5 were quite unoccupied

The insulin unit was transferred from the admission ward to the new ward, with the 6 patients receiving insulin

Opening the Unit

A few days before the unit was due to open, relatives of the selected chronic patients were invited to a meeting 47 relatives of 23 (of the basic 24) patients came At the meeting it was explained that we were opening a new ward for the social rehabilitation of young men Schizophrenia was not actually mentioned, but its effects in causing deterioration were discussed, as well as the effects of institution life, and a very cautious statement was made of plans and hopes The relatives were asked for their cooperation, especially over taking the patients home at weekends and at other times

The meeting was very lively and interested, and people repeatedly said how pleased they were to meet others with the same problems and to discuss mental illness without shame. They were extremely anxious to cooperate with the hospital, asked innumerable questions, and said they would like to meet regularly "to help our boys." They were pathetically grateful to us for consulting them, and constantly repeated that they wanted to work *with* us. Several offered to invite boys home who had nowhere to go, and there was much discussion (entirely spontaneous) about how they could help in finding work not only for their own relative but for his friends in the unit. It was agreed to meet again in two months.

The day before the ward actually opened, the 24 chronic patients were brought to a meeting, where it was explained to them that they were to be transferred to a new ward.

They showed little interest at first, sitting with bowed shoulders and apathetic rather blank faces. Most stared vaguely at their laps or turned their eyes up to the cornice with moving lips. They did not seem to listen or take much notice of each other, and looked a depressingly shambling stooping deteriorated set of typical long-stay mental hospital patients. The first response came when they were asked to take a good look at each other and say what they had in common. 6 immediately looked up, and very slowly the others gradually raised their heads and looked around in slow motion. Finally somebody said "We're all young", and several others agreed. From that moment they seemed to listen. It was explained very simply that it was hard on young men to be scattered in wards with elderly men who were not very active, and that we hoped to give them a fuller and more interesting life by concentrating the young men together, and that we wanted to help them regain their confidence and working capacity so as to fit them to leave hospital.

On the whole, the reaction was one of considerable anxiety—partly at having to make any change in their familiar routine, and partly at what the change might really mean. The better patients resented leaving snug, privileged positions and being grouped with the others, the more deteriorated showed a sort of primitive irritability at being poked. They acquiesced in a dreary resigned way to being moved but they did not care for the idea.

The unit started on its activities at a deliberately very slow tempo. We gave them a three-week settling-in period so that the mere fact of being together in a new ward should be all they had to contend with at first. During this time they continued at whatever they had been doing before transfer, working individually in various departments, attending occupational therapy, and so forth. The only change made in their routine was that, from the beginning, they had to make their own beds and join in doing all the ward chores, instead of leaving these to a few ward workers. No ward entertainments of any kind were provided. During this period the patients attended the clinical psychologist for individual assessment.

A weekly ward meeting of patients and staff, with one of the doctors acting as chairman, was initiated. By the second week the patients were growing restive and complained that life was dull and that nothing was done to entertain them. They were then invited to elect a committee of five, and it was at this point that they began to show the first signs of independent action and community feeling. They insisted that all 9 of the candidates nominated should form the committee. They declined our suggestion that a nurse on the committee might be helpful. When asked what they considered the committee's function to be, they surprised us by saying it was to organise work. We fell in with this assumption, and they immediately went into session. They refused to come out for meals, and more than three hours later emerged with a detailed rota for doing all the ward domestic work. This was a far better and wider scheme than anything the staff had envisaged. A striking feature was that it had been planned so that the more deteriorated patients were always put on duty with more capable ones.

During this first period patients kept complaining to nurses and doctors that there were no activities laid on. They were always given the answer that it was up to them to organise whatever they wanted through their committee, and that the staff would be glad to help. In this way, considerable social pressure arose, the pronoun "we" began to be used more often, and an astonishingly wide variety of activities developed.

At the end of three weeks the complete ward routine was introduced, following preliminary discussions with both patients and staff.

All ward domestic work is finished in time for the patients to put on working-clothes and to be out at work by 10 A.M. They knock off in time to get back to the ward and wash, ready for lunch at 1 P.M. In the afternoons there are various communal pursuits—e.g., play-reading, swimming, physical training, football, and cricket. Selected patients meet for group therapy once or twice a week. Thursday is a free afternoon. In the early evenings there are occupational-therapy hobby classes twice a week, and in the evenings a great variety of social events. Patients are encouraged to go out as much as possible and to go home at weekends. The insulin patients have their treatment during the morning but are drawn into general ward activities during the rest of the day. The staff meet weekly to discuss ward affairs, blow off steam, and settle policy. Frank criticism is encouraged, and this has done much to ensure smooth working together.

Work and Leisure

Our first project was to make a drive and gardens for the new occupational-therapy department.

The ground was extremely rough and full of iron and concrete posts, a concrete sunken shelter, a jungle of weeds, builders' debris, and a sort of artificial mountain resulting from the builders' excavations. The men worked hard and consistently, asked to see the architect's plans, and frequently discussed the job at ward meetings, making all sort of criticisms and suggestions. Even the most apathetic and withdrawn gradually began to do a little, though they needed a lot of encouragement. The nurses voluntarily worked with them, putting on denims and heavy boots, which is not the tradition in this hospital, and tactfully drawing into activity the apathetic preoccupied patients who tended to lean on a spade, listening to hallucinatory voices.

Our second project was the construction of a hospital car-park. We also undertook the destruction of some air-raid shelters, and the uprooting of a lot of fences no longer needed in a hospital with unlocked wards. The third project was a hospital road-widening scheme.

The response to all this hard navvying work was unexpectedly enthusiastic, the men seem to like purposeful physical activity and to enjoy both the destructive and constructive aspects of the work. They take a keen interest in the project as a whole and discuss it very critically. We have tried to foster this critical attitude by showing them the working drawings and by talking over the various difficulties as fully as possible at ward meetings. They take great pride in the finished job and are often to be seen showing their visitors what has been accomplished.

It was very interesting to see their reaction to being put on non-project work for a few days. Between projects the patients were asked to lend a hand, as individuals, in routine gardening. This work is productive and useful, but they all grumbled and obviously felt bored and discouraged Several explained that they wanted a job of their own, where they could work together and see what they had accomplished Patients are paid 5*s* 6*d* a week for their work (the rate in this hospital for ward and garden workers) There are occasional grumbles, and many jokes about chain gangs and the Burma Road, but most seem to realise that work is primarily treatment and only secondarily money-making Patients on insulin treatment are paid 2*s* a week

The patients take their duties of self-government very seriously and have made life so busy for themselves that sometimes they have difficulty in sparing time to be interviewed by their doctor At the weekly ward meeting the ward secretary reads the minutes, the treasurer gives his report, and the doings of the week are discussed and new plans considered When new activities are suggested, as they constantly are, there is usually quite lively discussion, and sometimes a vote is taken If something new is decided on, a patient usually volunteers to make arrangements and reports back the next week

The ward meetings follow a fairly set pattern We try to promote discussion and argument, while saying as little as possible ourselves We react less strongly to the occasional deluded ramblings than do the patients themselves, who become very restless and practically eliminate any contribution that is not strictly to the point We wait quietly through periods of silence but are not slow to close a meeting after 30–45 minutes when it is clear that nobody has anything more to say

Making money for the ward funds is a constant preoccupation Within two months the fund was up to £14 Money has been made by a tea-club which sells extra refreshments, raffles, a white-elephant stall at parties, and selling things made at the occupational-therapy hobby class The money is spent on theatres, football matches, and so forth, and there are also share-outs when patients go on leave at the end of a project

A parallel unit for schizophrenic women was opened about a month after the male one, and there is a great deal of joint activity This free mixing of the two wards grew up spontaneously The first move was made by the men, who wanted dancing-lessons, and on their own initiative invited the girls over for the first lesson This grew into a weekly informal dance Next the men invaded the women's cookery classes, the women came over to join the play readings (which are very dramatic affairs run by a professional coach), and soon the two wards had formed a habit of mixing socially on most days This was unpopular with quite a number of the men, who felt shy and nervous with women, but they have gradually come to tolerate their visitors and have even made friends

There are all the normal activities and games (table tennis, snooker, billiards, darts, football, cricket, and baseball), with whist drives, regular visits to the local swimming-baths, hobby classes, and cookery lessons (by the hospital catering officer) There are two or three socials a week, and our patients take a prominent part in hospital social life as a whole They are the most active members of the hospital social club and organised the hospital Guy Fawkes party they built the bonfire, set off the fireworks, and fed the company on roast potatoes There are also a skiffle group and a fortnightly ward newspaper In the summer the patients arrange a weekly outing, for which they are allowed to use the hospital coach, and it is left entirely to them to plan the outing and to finance it if necessary Most of the outings have been to Southend and other local places during the summer, but the patients have also been to Kew Gardens, Hampton Court, a circus, the Zoo, the Science Museum, and Wembley (to watch England *v* France), and have on several occasions made block bookings at theatres One play chosen was *Look Back in Anger*

Regular end-of-project parties are held These are organised entirely by the patients, who send out formal invitations to their relatives and friends The first of these ward parties, about five weeks after the ward opened, arose out of the promise at the first relatives' meeting to meet again in two months' time The party was a remarkable success, gave an excellent opportunity for staff and relatives to meet and talk, and showed the patients in a new light to their relatives, most of them acting very competently as hosts Further parties were clearly indicated, and it occurred to us to hold them at the end of each work project, with a week's leave after each

The projects are planned to last about three months Their completion is accompanied by a general feeling of pride and satisfaction, and it is fitting to mark this by a kind of end-of-term celebration The leave period is useful in several ways Mild pressure can be brought to bear on relatives who seem unreasonably reluctant to have patients home It is a convenient landmark at which to discharge the occasional patient, this is mainly useful with short-stay patients and can be a lever to dislodge some or to hold others for those few weeks longer which may be desirable Above all it breaks up the dreary interminable succession of months which in an institution follow one another without interlude or highlight We hope it may have some effect in restoring a form of rhythm to patients' lives and possibly combat the time distortion of the chronic schizophrenic Usually more than half the ward go on leave at this time, thus giving the staff a brief opportunity to concentrate on the more deteriorated patients who are left these enjoy a week in which they get all the attention

When insulin patients first join the unit, the long-stay patients are extraordinarily tolerant of the extravagances of the acutely ill, draw them into ward activities, watch over them for signs of secondary coma, and give them constant encouragement As the insulin patients improve, they in their turn contribute to the community They take a leading part in organising activities and bring their outside interests into what might otherwise be a too self contained little group Insulin treatment is followed and accompanied by social training, and valuable continuity is achieved with none of the trauma that so often accompanies a patient's transfer from the insulin unit to a convalescent ward

Putting the insulin unit into this open ward, which lacks the staff necessary for 24-hour continuous observation of patients in bed, gives rise to certain difficulties Some acutely disturbed recent admissions have been too unreliable for such a ward and have had to be treated elsewhere until electroconvulsive therapy, chlorpromazine, or the healing power of Nature has made them socially suitable for insulin-shock therapy Others, who continued too disturbed for the ward, have had to be denied insulin-shock therapy even when it was considered the treatment of election

New entrants to the unit, whether for insulin or for social therapy alone, have come through other wards They are always vetted by one of us, and there is no direct admission

The influence of other patients in social therapy is proving very valuable

A good example of this is the Junior Supper Club About 12 of the better preserved patients meet informally in the kitchen most nights for a little supper which they buy and cook for themselves on a communal basis This has been nicknamed the Senior Supper Club One member organised what he calls the Junior Supper Club For this he gathered together the 8 or 9 most deteriorated patients—the withdrawn apathetic ones who join in very little and would certainly not agree to pool their money for supper He draws them together each evening, makes them toast and hot milk, and often provides more at his own expense After months of persistent effort the Junior Supper Club now assembles fairly spontaneously, and some of its members now help to make the toast, wash up, and begin to show a very little social feeling

Staff and Patients

The great stress laid on maximum communication between patients, nurses, relatives, and doctors makes it possible to foster and recognise—as well as tolerate—the first stirrings of initiative Great skill and patience are needed on the part of the nurses to guide the reviving patient into socially acceptable modes of expression This means that the ward offers an exceptionally good training-ground for the student nurses who come to us for up to three months at a time Their curiosity and receptivity are very valuable to the unit, and we ask them to make a careful study of particular patients They then present their observations to the ward staff meeting, and in this way patients are reassessed, and plans for treatment are made by the meeting as a whole This means that the long-stay patients with great folders full of forgotten notes are considered again as though they were new problems, and this often produces a new approach which is helpful to the patient

Of the 24 founder members, 5 have had to be transferred to other wards, 2 because they ran away repeatedly, 1 became intolerably aggressive, 1 impulsive, and 1 negativistic enough to be a bad influence 2 others did not return from leave and had to be left at home with our blessing if not our approval

There is a steady flow of discharges of short-stay patients, and the first 3 long-stay patients have now started work at a nearby factory, while continuing to live in the unit for the time being A 4th (the organiser of the Junior Supper Club) has just joined an Anglican monastery as a resident lay worker

This partial withdrawal of 4 of the best-preserved and most active long-stay patients has stimulated initiative in some of those who were content to be organised by them New leaders, though of rather inferior calibre, have begun to appear and take their work as committee members very seriously 3 or 4 patients show no improvement, do not cooperate, and try to avoid their share of communal chores They are much resented by the others and are often publicly criticised, but so far the community continues to tolerate them

Discussion

Living in a self-governing community and working as a group on socially useful projects has had a marked effect on the patients, which is commented on spontaneously by all who know them, especially their relatives "Even the goldfish are more active in this ward" is our most precious testimonial The patients themselves say that life is much more enjoyable now, and many comment on feeling fitter and more confident They look smarter and brisker, talk more spontaneously, and are altogether more responsive With a high proportion of those who have been severely damaged by their illness, this may well be all that can be achieved We hope, however, to return the others to the community

It is difficult to quantify the improvements observed or to assign cause and effect accurately, but there seems to be little doubt that we have established not only a happy ward but also one with therapeutic powers These therapeutic powers seem to depend to a very considerable extent on having the same nurses on the unit long enough to establish a real relationship, and on having enough of them Sometimes, when the hospital has been short of staff, we have had frequent changes, with nurses coming for short periods as reliefs These times have been marked by a sagging ward morale with a tendency to return to aimless drifting, and a failure to cultivate the patients' initiative A nurse doing this kind of work needs the same sort of patience as a mother who lets her 3-year-old do up his own buttons

Many of the chronic patients who have improved so much in bearing, work, and apparent social adjustment, retain intact their delusions and disordered modes of thought The King of the Incas, while retaining his imperial status, now works quite well, joins in the discussion, and looks neat and relatively brisk, compared with his former slouching idleness only relieved by occasionally toying with a little basket-work This suggests that much of the typical "chronic patient" appearance and behaviour is due to hospital conditioning, and is not necessarily an inescapable consequence of the primary illness The long-stay mental-hospital patient is all too likely to lose his human dignity through giving up his own responsibility for himself, and in our unit we are trying to prevent this happening

Summary

Our experience in starting a new schizophrenic unit on community lines is described We have tried to improve certain aspects of the care of long-stay patients in a hospital where (if we may say this, being only short-stay doctors) the standard of such care is already high The essential principles involved are (1) an attempt to reproduce normal stresses by introducing compulsory work and democratic social organisation, (2) bringing the families into the treatment situation, (3) maximum communication, (4) selective mixing of acute and chronic cases for mutual benefit

The preliminary planning and the mechanism of opening the ward are described, followed by a general account of how things have worked out during the first year

We are indebted to Dr G Somerville, physician superintendent, and Dr J E McA Glancy, consultant psychiatrist, for their help and encouragement as well as to Miss J Stapleton, clinical psychologist, Miss Abley and Miss S MacNulty, psychiatric social workers, and Miss M D Beldam, head occupational therapist, for their valuable assistance

THE HEALTH SERVICE IN 1957

LAST year, perhaps the most important event bearing on the National Health Service was the publication of the report of the Royal Commission on the Law relating to Mental Illness and Mental Deficiency [1] One of the Commission's recommendations—that mentally defective patients should be compulsorily detained in hospital only when this is positively necessary for the patient's own welfare or for the protection of others—has already been acted on [2] In his introduction to the Ministry of Health's report on the year,[3] Mr Derek Walker-Smith, the Minister, says that he looks forward to new legislation "as soon as the difficulties and complexities of the subject permit"

DEMANDS ON HOSPITALS

The annual report shows the year to have been one of solid endeavour The hospitals of England and Wales treated some 55,000 more inpatients than in the previous year, the total being 3,794,000, but waiting-lists, which had been falling in previous years, increased by about 9000 to 440,000

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[1] Report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency H.M Stationery Office, 1957 See *Lancet*, 1957, i, 1187

[2] Circular H M (58)5

[3] Report of the Ministry of Health for the year ended Dec 31, 1957 Part I 1 The National Health Service 2 Welfare, Food and Drugs, Civil Defence Cmnd. 495 H M Stationery Office 1958 Pp 254 12*s*

Last year some 29% more patients were treated than in 1949, though the number of beds was only about 6% greater than at the start of the service

At the end of the year patients awaiting admission to general-surgery departments numbered 131,000, and those awaiting admission to ear, nose, and throat departments numbered 104,000, these two departments thus accounted for more than half of the total waiting-lists The extent of waiting-lists differed greatly between England and Wales and between regions in England In Wales, only in traumatic and orthopædic surgery and in "other" departments were there increased waiting-lists In England, the demand for admissions to hospitals in the Oxford region continued to increase, in contrast, the overall position improved somewhat in the Manchester and Liverpool regions, and waiting-lists increased less than average in East Anglia

In general, both the London and provincial teaching hospitals have much larger waiting-lists in relation to their resources of staffed beds than the non-teaching hospitals

Compared with the non-teaching hospitals, about three times as many patients were awaiting admission to the general medical departments of London teaching hospitals, and three and a half times as many to the same departments of the provincial teaching hospitals For general-surgery departments the difference between the London teaching and non-teaching hospitals was not so great, but at the provincial teaching hospitals the waiting-lists per 100 staffed beds were about two-fifths greater than at the non-teaching hospitals

At the non-teaching hospitals most major departments except ear, nose, and throat, and at the teaching hospitals most departments except ear, nose, and throat and gynæcology, treated more patients per available bed than in 1956 This was due in nearly every instance to reduced stay in hospital, and not to reduced interval between occupation of beds

The number of inpatients admitted to designated mental hospitals was 88,943, of whom 73,499 (82 6%) were voluntary patients, 1318 (1 5%) temporary, and 14,126 (15 9%) certified The total in 1956 was 83,994, of whom 65,637 (78 2%) were voluntary, 1453 (1 7%) temporary, and 16,904 (20 1%) certified

The number of patients admitted to mental hospitals has been rising steadily for many years—the number increased by some 5000 in 1957—but the number of patients resident has begun to fall, owing to the rehabilitation and discharge of patients who have been in hospital for many years, and the shorter stay of newly admitted patients In 1957 the national average of overcrowding, which had been 14% in 1956, fell to 11 9%

HEARING-AIDS

During the year 52,166 new patients were fitted with hearing-aids, bringing the total fitted with aids since 1948 to over 580,000 Following field trials orders were placed for the first batch of 'Medresco' transistor hearing-aids These aids, which weigh just under 3 oz complete with battery, compared with $24^1/_2$ oz with battery case for the original model issued in 1948, are intended in the first instance for children and will not be available to adults until 1959

BLOOD-TRANSFUSION

The strength of the civilian donor panel in the National Blood Transfusion Service amounted to 674,117 at the end of the year, compared with 639,319 a year earlier The number of donations rose from 803,522 in 1956 to 846,202 in 1957 The attendance-rate of general-public donors invited to give blood remained unchanged at an average of 51 8%

CONSULTANTS

Consultants in the National Health Service, including those employed by the Board of Control and in the Public Health Laboratory Service, numbered 6902 at the end of last year, compared with 6739 at the end of 1956 and 5649 at the end of 1950 The numbers receiving distinction awards were as follows A (£2500 per annum), 276, B (£1500), 690, C (£500), 1377

GENERAL MEDICAL SERVICES

During the year the number of doctors admitted to executive councils' lists was 936 and the number deleted was 694 Of those admitted, 601 entered into partnership, including 310 assistants who joined their former principals The total number of doctors practising as principals and providing unrestricted general medical services in England and Wales at July 1 increased from 19,082 in 1956 to 19,343 in 1957 The number of single-handed practitioners (including those with assistants) continued to decline—from 6568 in 1956 to 6381 in 1957 The number of assistants (excluding trainee general practitioners) at July 1, 1957, was 1465, compared with 1546 in 1956 The general decrease in assistants which seemed to have been arrested in 1955 and 1956 has now been resumed

There was a further decrease in the number of patients living in under-doctored areas from 9,500,000 in 1956 to 8,500,000 in 1957 The average number of patients per doctor remained virtually the same—2273, compared with 2272 in 1956

GENERAL DENTAL SERVICES

From 1952 onwards the volume of treatment given under the general dental services increased at the rate of 8–9% a year, but in 1957 the increase over the previous year was only 5 2% This was nevertheless appreciably more than the increase in the number of dentists in the service (2 3%) At the end of the year 16,113 dentists were on the Dentists Register, compared with 16,007 at the end of 1956

EFFECTS OF RADIATION

M R C Committee's Comments on U N Report

THE committee appointed by the Medical Research Council to report on the hazards to man of nuclear and allied radiations has prepared a statement [1] on the United Nations report published last week [2]

In general the U N report follows the same lines as the reports of the M R C committee and the United States National Academy of Sciences, both of which were published in 1956 "We have derived considerable reassurance", the M R C committee say, "from the fact that, in a field of science that is so difficult and, as yet, relatively little developed, the three major reports on this subject are so substantially in agreement with each other" In the past two years much additional information has been collected, but it has led to no major revisions of opinion "rather it has strengthened and amplified the tentative conclusions and predictions in the two earlier reports" Both the 1956 reports confined their attention to conditions in technologically well-developed countries of the Western world the U N committee has considered the problem on a worldwide basis

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[1] *Statement on the Report of the United Nations Scientific Committee on the Effects of Atomic Radiation* H M Stationery Office Cmd 508 Pp 15 1s

[2] See *Lancet*, Aug 16, 1958, p 360

DOSE AND EFFECT

From their reading of the U N report, the M.R C committee derived the impression of a predisposition to favour the view that induction by radiation of such possible long-term somatic effects as leukæmia and cancer was a process comparable to that of induction by radiation of genetic mutations, and that there was, in consequence, no threshold dose below which there was no induction of such somatic effects "In our opinion, this view tends to tinge the interpretation of subsequent data, despite the earlier recognition of the equally tenable alternative view" The M R C committee add

> "In our view, it is not possible at this present time to decide whether there is or is not a threshold dose concerned in the induction of leukæmia and cancer, and the only scientific attitude to the problem at present is one of suspended judgment Nevertheless the significance of the alternative points of view in determining the ultimate assessment of risk should be clearly understood so that those who have the responsibility for acting on such assessments should be fully aware of the alternative possibilities that need to be taken into account"

GENETIC EFFECTS

The M R C committee accept the view that the knowledge now available indicates that "there is at present no known threshold of radiation exposure below which genetic damage does not occur", that "the experimental foundation for a linear dose relationship is fairly well established at moderate doses but is increasingly meagre at lower doses", and "that it is prudent to assume as much hazard as is implied by a linear relation between mutation and gonad dose"

In the difficult matter of estimating the amount of radiation required to double the mutation-rate of a representative number of human genes the U N committee arrived at a range of possible values similar to that put forward in the M R.C report They suggest a range of 10–100 rad, compared with the M R C's figure of 30–80 rad

DIAGNOSTIC IRRADIATION

Both the 1956 reports drew attention to the large contribution made by medical diagnostic irradiation to the genetically significant population dose The M R C committee had put this contribution at some 22% of the natural background, with the reservation that this figure should be regarded as tentative and probably a lower limit They now say that "further information has confirmed us in this reservation so that we are now willing to accept that the genetically significant dose from this source may be as much as 100 per cent of the natural background radiation in countries with extensive medical facilities" It is reassuring to note, they add, that there is agreement that most of this genetically significant dose comes from a few types of radiological examinations

FISSION PRODUCTS

Since 1956, it has become recognised that the deposition of fission products from the reservoir in the stratosphere is not uniform over the globe, but that countries between 30° and 50° N may receive a deposition about three times greater than the worldwide average In this country the annual fallout-rate of ^{90}Sr has increased very little since 1954—from 2 to 2 5 microcuries per sq km In New York State the increase has been from 3 to about 4 5 microcuries per sq km

The U N committee concluded that, for the same degree of fallout, the average concentration of ^{90}Sr in the bones of those living on a plant-type diet may be up to 5 or 6 times that in the bones of those on a milk-type diet The M R C committee consider that, on the available evidence, this is a reasonable conclusion, and they think that the methods chosen for calculating future fallout levels are also reasonable, "but the soundness of the conclusions reached necessarily depends on the validity of the initial assumptions"

ASSESSMENT OF THE HAZARDS

In 1956 the M R C committee said that the maximum allowable concentration of ^{90}Sr in the bones of the general population, with its proportion of young children, should not be greater than 100 strontium units (S U) The special subcommittee of the United States National Academy of Sciences appointed to consider this matter were unable to reach agreement, but the general belief was that 50 S U would produce no perceptible effect. The M.R C report said that immediate consideration would be required if the level in the general population showed signs of rising greatly above 10 S U The mean marrow fallout doses over 70 years given in the U N report are equivalent to strontium levels ranging from 2 3 S U as the average in bones of people on a milk-type diet (assuming weapon tests stop at the end of 1958) to 240 S U in bones of those on a plant-type diet (assuming weapon tests continue under certain hypothetical circumstances until equilibrium is reached in about 100 years) The significance to be put on these figures depends on the existence or absence of a threshold, and "in the present state of knowledge it is not possible to decide between these alternatives"

HOSPITAL ADMINISTRATIVE AND CLERICAL STAFF

AT the end of last year, in a report to the Ministry of Health and the Department of Health for Scotland, Sir Noel Hall recommended revision of the grading structure of the administrative and clerical staff of hospitals [1] The Ministers referred his proposals to the appropriate Whitley Council. The management and staff sides accepted Sir Noel's proposal that the seven existing lettered grades A–G should be replaced by the following five new grades clerical, higher clerical, junior administrative (which is to be a training grade), general administrative, and senior administrative

The salary scales of the present grades are

A1	£206–£453	D	£556–£659
A2	£206–£515	E	£623–£753
B	£299–£546	F	£693–£862
C	£515–£597	G	£802–£983

The scales for the proposed new grades, which have been accepted by both sides of the Whitley Council, are

Clerical grade	£230–£600
Higher clerical grade	£575–£735
Junior administrative grade	£575–£725
General administrative grade	£750–£1000
Senior administrative grade	£1000–£1240

The management and staffs sides were, however, unable to agree on the manner and pace of introducing these changes, and the disagreement was referred to the Industrial Court. By their recent award [2] all staff are to remain at their present rate of pay until each employing authority has reviewed certain posts according to the new grading structure, this review is to be completed before Nov 1

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[1] *Lancet*, 1957, ii, 1104

[2] Industrial Court (2701) National Health Service.

Salaries will be raised to the new rates in stages The first increase will be retrospective to July 1, 1958, and the new rates must be completely introduced by July 1, 1959, for the clerical grades, by July 1, 1960, for the general administrative grade, and by July 1, 1961, for the senior administrative grade Immediate increases will vary from £22 to about £100 a year

Negotiations on "designated" posts, including hospital secretaries, are continuing The award affects only hospital officers and does not apply to other National Health Services clerical and administrative officers such as those serving executive councils

Public Health

Cholera in Asia

Cholera has broken out in Khatmandu, Nepal This is the first cholera epidemic reported in that country since the beginning of the century

The cholera situation in Asia, according to W H O, is the most serious in years Cases and deaths are twice as numerous as last year in India and East Pakistan, and an epidemic has struck Thailand for the first time for many years Cholera has also been recorded in Cambodia and Burma Cumulative totals up to July 31 were as follows

	Cases	*Deaths*
India	29,372	12,851
East Pakistan	10,386	6644
Thailand	8964	1190
Cambodia	3	0
Burma	4	2
	48,729	20,687

The Indian Minister of Health said last week[1] that more than 16,000 people had died of cholera and smallpox in Bihar and West Bengal in the first six months of this year Smallpox was also epidemic in Uttar Pradesh but figures were not yet complete Unofficial estimates put cholera deaths in the Katmandu Valley of Nepal at more than 300

No Fluoridation in Worcestershire

The public health committee of Redditch accepted the medical officer of health's recommendation to put fluorine in the town's water-supply, and similar decisions were reached by the two Bromsgrove councils, who also receive water from the East Worcestershire Waterworks Company But the company has rejected their requests because it is uncertain about the legal situation The manager is reported[2] to have said that his board had decided to take no action until the results of the Ministry of Health's experiments in three other test areas (Watford, Kilmarnock, and Anglesey) were announced "I doubt whether there is a single undertaking in the country that would take any notice of such appeals until the Ministry report is issued," he added The decisions at Redditch and Bromsgrove had not been met by any such organised protest as led Andover Borough Council to stop the testing of fluoridation[3]

Mustard Gas Burns?

On Aug 4 two young men were walking with a dog on the Western Heights, Dover[4] The dog apparently burned its mouth while in some long grass, and later it had to be destroyed Next day a rash appeared on the arms of the two youths They went to hospital, but were not detained The possibility that they came in contact with mustard gas is being investigated, but this explanation is now thought unlikely

In England Now

A Running Commentary by Peripatetic Correspondents

The second brood of swallows are well on the wing There has not been time for a third this year I am no ornithologist. the swallows have always been just part of our pattern of lif and have shared this house with the dalesmen who watche before us for the past four hundred years I do not understan why they should choose to come back or how they do it ther are some things over which one should rest content About th beginning of April, when the first lambs are being born aroun us in the valley, we start to look down the long silver ribbon o Windermere for the silhouettes of wavering flight out of th warming sun The winters are long in Lakeland, grim an austere on the fells The swallows mean more to us than bird returning It was April 21 when they came this year th Queen's birthday, the day the children came back fro abroad, the day the sun was shining Back to the same set o nests in the stable, the twittering around the chimney pots the curving flight to the beck for mud to mend the lip of th nest, the pantomime of courting, and then down to seriou business on a clutch of eggs

For as long as I can remember the stable has held just on pair of swallows they surely cannot be the same pair year afte year How do they decide which ones shall inherit the nes next season? Eight or a dozen youngsters fly away in autumn two birds come back in spring No fighting for possession, n queuing up, no ribbon development along the stable beam Somewhere and somehow these things must be decided perhaps around the pillars of the Parthenon on Christmas Day, perhaps along the timelessness of the Nile Two birds come back in spring There are days when I should like to know the answers Where the rest of them have gone? How many seasons one pair are here? Ring them with metal bands? But my heart would rather not know For who were all the people laughing through this house for its four centuries on the fellside, watching the swallows where did all their children go, and how was it handed down? They are gentle ghosts who deserve their rest Who will care in 2358 for the brief season of our day? They will watch the swallows still The second brood are well on the wing I know now when they will go It will be the third week in September the week when eighteen years ago the sky was weaving with the swooping tumbling flight of youngsters to decide who should come back to England in the spring

* * *

I came into our hospital the back way the other morning (my usual short-cut between the departments of psychiatry and radiotherapy) and saw, standing between these two buildings, the back half of a red double-decker bus Nobody knew how it had got there, or who put it there, or why, and speculation ran wild

Perhaps it was something to do with the bus strike—the busmen cutting off half their bus to spite the other half, or was it a rather embarrassing gift from one of the inhabitants of the nearby Fen villages who had run amok with a large saw, and was distributing half buses here and there to his friends and acquaintances?

We thought it might be connected with radiotherapy, as it stood between their main building and the shed which houses their precious noisy and extremely temperamental synkrotron Was it, perhaps, a new synkrotron, heavily disguised, one that did not need a lead wall around it, 6 ft thick, or the ministrations of two full-time highly qualified physicists and their minions to coax a few hours' work out of it weekly? But the radiotherapy director disclaimed it

The most likely explanation seemed to be that it was some sort of psychotherapeutic aid—a solid symbol on which the patients and psychiatrists could hang their fantasies The castrated appearance of the bus was thought to support this view But the psychiatrists were as mystified as the rest of us

The explanation turned out to be straightforward and slightly disappointing The half bus was a present from the local coach company to the department of physical medicine to help in the rehabilitation of their patients, and its final home is outside physiotherapy, where it looks both useful and decorative, with a red rose in a tooth-mug at the foot of its stairs

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[1] *Times*, Aug 18
[2] *Ibid* Aug 16
[3] *Lancet* July 26, 1958, p 204
[4] *Times*, Aug 15

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The Neo-medical Travel Agency has been closed. I really cannot understand why To say the least it is unfortunate for we had a very satisfied, well-informed clientele

We used to take our clients as far as mid-Channel before putting them under (with hypnotism I mean), but we soon realised that we could cut expense by not transporting them at all, so they just used to come to the agency We bundled them upstairs, luggage and all, laid them down, and put them under, and there they lay for their time—two or three weeks, whatever their holiday period was We tube-fed them, nursed them carefully, gave them twelve hours' sleep and twelve hours of movies (full-colour local views including the hotel) We played them tapes with all the relevant local vital statistics, which made them the most knowledgeable travellers of an agency, and they all turned out nut-brown with judicious dosing with ultraviolet rays (no painful burns or peeling)

It was a pleasure to watch them at the end of their time going forth, their minds full of the pleasures of France, Spain, Greece, or wherever they thought they had been, well fed, well tanned, and well rested Quite a contrast to the peeling, harassed, confused traveller of other agencies who needs a fortnight's rest to recuperate from his holiday

Just because we couldn't get one under, all the rest have to suffer We tried to explain to him, but he wouldn't be reasonable He reported us to the authorities and they closed us It is all most disappointing, and I really cannot understand their attitude I was going to say "it's a strange world," but some of us have now come to feel that there really isn't anything farther than mid-Channel

* * *

Once again my hayfever season has ended and the year's "most effective ever" drug has been assessed It did not seem to make a great deal of difference to my streaming nose and eyes, but at least it did not send me to sleep (The fairly early end of my surgical career may well have been influenced by the fact that on one bright July day, when well dosed with the latest antihistamine drug, I began to snore in the operating-theatre) In early summer people ask my advice about treatment They wait patiently while I try to find one of my five handkerchiefs, then sigh resignedly and go away One day last month I was sneezing happily away in the train, when I had a disturbing thought "You just look ridiculous, my friend" Observe the method, no thought of treatment, no concern, and certainly no sympathy Within minutes the attack had ended and since then I have found the result can be repeated Perhaps this new approach is a good one, or perhaps the latest wonder drug deserves more credit than I have given it

* * *

An octogenarian Yorkshire lady stopped me in the street one day "Hey doctor! My granddaughter's got spots on 'er face You know the name The one like 'orses and carriages What d'yer call it? Oh, yes, acne" Or does she spell it 'ackney?

* * *

Problems of irradiation
Are disturbing every nation
Bent on human preservation
Genetic hazards must be measured
If fertility is treasured.

People potter round with counters
That they cannot understand,
Write alarmingly to papers
About death upon the land.
They know nothing of the meaning of the röntgen and the rem,
The rep and rad are so much Greek to them
And when faced with R.B.E
They are hopelessly at sea

But mutation of the gene
Doesn't worry Aberdeen
It will populate the planet
In despite of rays from granite

Letters to the Editor

CHILDREN IN HOSPITAL

SIR,—The provision of a satisfactory hospital service for children concerns us all The report set out by the Royal College of Physicians (April, 1957) to guide "individuals and authorities who are planning the care of children in hospital" has been sadly overlooked It stated that "there is no doubt that special children's hospitals offer the best service for children because the staff at all levels and in all departments is attuned to the special needs of the sick child" Pædiatric physicians and surgeons must be grateful to Professor Illingworth and to *The Lancet* for its leading article (July 26) for re-emphasising these needs to the medical world, and to Mr Denis Browne and Dr Helen Mackay for bringing the facts before the public through correspondence in *The Times* (Aug 6 and 11) The threatened closure of children's hospitals strikes horror in the hearts of those who can best understand the special needs of ill children

For a long time cold war has existed between children's hospitals and fever hospitals, but, now that Dr Emond (Aug 9) tells us that fever units admit, and should admit, cases of pneumonia and meningitis, he shows how false is the separation of patients into these two special hospitals - Pædiatric units admit these cases too, and a children's hospital with suitable isolation facilities for "infectious diseases and notifiable infectious diseases" could provide a comprehensive hospital service for children in which specialists in all branches of pædiatric medicine could cooperate The Ministry of Health stated[1] that "it is of the utmost importance that hospitals and wards for infectious diseases should be closely associated with pædiatric departments" and the Royal College of Physicians report endorses this view and urges that pædiatricians be appointed to fever hospitals when vacancies arise and that blocks for infectious fever should be included in the development of large pædiatric units This will not come to pass if the Minister pursues his policy of closing children's hospitals URSULA JAMES

SIR,—I am delighted to know, from Mr Braithwaite (Aug 16), that the South West Metropolitan Regional Board no longer intend the immediate closure of Queen Mary's But this is news On July 23 the chairman of the regional board, Mr A G Linfield, told the chairman of our management committee, Major H J Wells, that it was the intention to "run Queen Mary's down" over the next few months and that the Fountain Hospital would move in early in 1959 The chairman of the Surrey and West Sussex area committee of the board, Major-General L A Hawes, was present at this interview, but Mr Braithwaite was not If any charge of inaccuracy is to be made, therefore, it should not be directed at me

Mr Braithwaite's second charge contains a half-truth The chairman did refuse, as I reported in my letter of Aug 2 to entertain the idea of getting expert pædiatric advice It was *after* this that the board had second thoughts, and invited Professor Moncrieff I entirely concur with the views in Mr Braithwaite's last paragraph, but the inaccurate and intemperate statements have not been mine Personal attacks will not deflect me, or I hope others, from sober and careful study of this important issue in all its aspects

Queen Mary's Hospital for Children,
Carshalton, Surrey

DAVID LAWSON
Physician-Superintendent.

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[1] R.H.B 48 1

UNSATURATED FATS AND IMPORT RESTRICTIONS

SIR,—Recent work has established a high probability that human arterial disease is influenced by dietary fats, and has proved that the replacement of saturated fats by polyethenoid oils tends to reduce the cholesterol content of human serum [1 2] Since a dietary change of this type is almost certainly harmless, and safer than any excessive restriction of fats, it seems desirable to advise patients with raised blood-pressure or anginal pain to make this change as far as is reasonably practicable Thus butter and cooking-fats may be replaced by corn oil (from maize), or by the more expensive sunflower or safflower oils, and the saturated fats may be further reduced by substituting skim-milk powder and skim-milk cheese for the normal products

I find, however, that patients in Britain are unable to purchase corn oil, and have difficulty in finding other flavourless oils with a high content of polyethenoid acids On inquiry from a leading London store I am informed that, owing to Board of Trade decisions on goods requiring dollars, " corn oil does not at present figure in goods to be bought from abroad "

It would, I suggest, be helpful to the numerous British people suffering from arterial disease (and possibly those from certain other serious diseases, as suggested by Sinclair [3]) if some correspondent would mention in your columns such edible " unsaturated " oils as can be bought retail in Britain, and their average content of linoleic or other polyethenoid acids If no refined oils are available, except olive oil which is useless for this purpose, and West African groundnut oil which is described by Hilditch as low in content of linoleic acid,[4] could the medical advisers to the Board of Trade consider allowing the import of corn oil from Canada or the U S A ? It seems at least possible that this would reduce the rate of ageing of some of the most active people in the nation

Ganges,
British Columbia,
Canada

R B BOURDILLON

MODIFICATION OF EGG-YOLK FATS

SIR,—The forcing of domestic poultry to consume sunflower seeds instead of those grains which are natural to them, in order that human beings may themselves consume an unnatural product in the form of their eggs so altered, breaks every evolutionary law and can therefore never hold the solution to the problem of coronary disease

I have tried to point out in a small publication [5] that the Darwinian theory of evolution teaches us that we should consume those fats that we individually like, whether animal or otherwise, in just the amounts we desire, always assuming that the fats have not been greatly altered from their natural state or so mixed with other foods that we are unaware we are eating them

Securing an unnatural product by the means described in your issue of Aug 2 (p 243) is therefore doomed to failure from the start How can the tactics be correct when the overall strategy can be proved to be incorrect? How can the tree be right when the wood can be proved to be wrong?

Gosport, Hampshire

T L CLEAVE

INTRACUTANEOUS RIBONUCLEASE IN CHRONIC MYELOCYTIC LEUKÆMIA

SIR,—In the blood of patients with chronic myelocytic leukæmia I have observed many dead and dying leucocytes Dead leucocytes may stimulate proliferation of bone-marrow I have shown that the urinary ribonuclease activity of patients with chronic myelocytic leukæmia is several times higher than that of normal persons [1] It seems that the tissues of these patients lose this enzyme abnormally, consequently enzyme autolysis of granulocytes is diminished Perhaps that is why many dead leucocytes are present in the circulating blood

I have made good the deficiency of ribonuclease by injecting it intracutaneously (0 5–1 mg daily) in patients with chronic myelocytic leukæmia The leucocytosis diminished, the spleen became smaller, and the general condition of the patients improved Further researches are in progress

IIIrd Clinic for Internal Diseases,
Academy of Medicine,
Kyakow, Poland.

JULIAN ALEKSANDROWICZ

A WATER-SOLUBLE DRESSING GAUZE

SIR,—Gauze impregnated with a soft paraffin, and made up in boxes which can be sterilised and sealed, has long been used for all types of wounds It can be produced in many different sizes and is easily handled From the patient's point of view, the dressing does not stick, nor does it cause discomfort It can be used both on superficial lesions and in deep cavities I have used it extensively in the casualty department of the Bristol Royal Infirmary

In a busy department I have tried to simplify the dressing routine as far as possible Sterile paraffin gauze was used as a dressing for burns, incisions, and most abrasions and open wounds Other dressings are used also, but paraffin gauze was widely employed

It was found to have some disadvantages The soft paraffin adheres to instruments and gloves and makes them greasy so that wool or other materials stick to the forceps or hands It cannot be washed off by immersion in sterile water unless it is either very hot or contains some solvent for soft paraffin In many cases wounds which were dressed with paraffin gauze for more than about five days became very moist and the granulation tissue very unhealthy and œdematous The skin edges became wet and in some cases these became reddened and even blistered, preventing the control of infection and so delaying healing There were some wounds in which a spread occurred from the lesion to normal areas—a most irritating and alarming procedure for the patient This could be prevented by reducing the length of time the paraffin gauze was employed, and by taking care that only one layer was used It very soon became obvious that gauze which was over full of soft paraffin was more likely to cause trouble

Moreover, the cleansing of the wound became very difficult The paraffin on the skin around the wound must be removed thoroughly but this can be done only by fairly heavy and repeated swabbing

In cooperation with Mr G H Darling, our chief pharmacist, a dressing gauze which seems to have all the advantages of paraffin gauze, without its disadvantages, has been developed To keep the wound dry one must have a gauze that will mix with both the serum of the wound and the skin secretions It must not block the openings of the sweat glands It must not stick to the wound and it should be easily removed from gloves and instruments

The macrogol gauze,* which we have used for approximately

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[1] Keys, A , Anderson, J T , Grande, F *Lancet*, 1957, ii, 959
[2] Rutstein, D D , Ingenito, E , Craig, J M , Martinelli, M *ibid* 1958, i, 545
[3] Sinclair, H M *ibid* 1956, i, 381
[4] Hilditch, T P The Chemical Constitution of Natural Fats London, 1956
[5] Cleave, T L Fat Consumption and Coronary Disease an Evolutionary Approach (with a foreword by Dr Percy Stocks) Bristol, 1957

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[1] *Lancet*, 1958, i, 641

* *The macrogol gauze base being used consists of*

Polyethylene glycol 300	15 oz
Polyethylene glycol 1500 GEN	3 oz
Polyethylene glycol 4000	2 oz

This gives a conveniently firm dressing that softens readily at body temperature eighteen months, is not harmful to the tissues, does not stick, and is water-soluble Because of this the moisture in the wound and surrounding skin can pass through the gauze into the dressings outside it It does not make the skin moist, and delayed healing and sensitisation are therefore unlikely It can be prepared and used in a similar manner to paraffin gauze It is easily removed from the hands, instruments, or the patient's skin, by gentle swabbing with water or saline It causes a minimum of inconvenience for the dresser and of discomfort for the patient

We have used it for both daily and less frequent dressings and it does not appear to delay healing nor does it give rise to any unpleasant odour The macrogol gauze can be prepared with any desired percentage of an antibacterial agent We have used it with 0 2% nitrofurazone in it, but this was abandoned when reports of sensitivity appeared.

Many people are dissatisfied with preparations of soft paraffin gauze and I am sure that these difficulties must have been overcome in a diversity of ways, but in our experience macrogol gauze is a very satisfactory dressing with a wide range of application

After clinical trials had shown the gauze to fulfil all the claims made for it, we gave the formula to Messrs Smith & Nephew, and we are now using their preparation called 'Carbonet'

Bristol H K BOURNS

AN UNUSUAL SOURCE OF MERCURY IN PINK DISEASE

SIR,—The relation between mercury and pink disease has been much discussed, and though the consensus of opinion seems to hold that a direct causal relationship is "not proven," there is good evidence that the frequency of the association is more than incidental The sources from which infants may absorb mercury are usually fairly well defined (teething powders, mercurial ointments, vermifuges, &c) The case described here seems to be of interest since it involves an unusual source of mercury absorption in the infant

A boy child, aged $2^{1}/_{2}$ years, was admitted to the Hospital for Sick Children, Great Ormond Street, under the care of Dr Wilfrid Sheldon, in May, 1958, after a series of epileptiform convulsions He was a third child, and there was no history of birth trauma nor any family history of neurological disease or fits

His development had been possibly slightly retarded (he sat up at ten months, walked at twenty months, and at the age of two years spoke only a very few single words), but he had been otherwise well until October, 1957 At this time the whole family had influenza, and he had an acute pyrexial illness and a convulsion. He was admitted to the local hospital but made a quick recovery and no abnormality apart from his mental slowness was noted

The child remained well until April 29, 1958, when quite suddenly he had a series of convulsions which continued for thirty-six hours until controlled by sedation He was admitted to a local hospital where it was thought that he had become both deaf and blind and where a lumbar puncture was performed and found to be normal

On arrival at Great Ormond Street he was fully conscious but very irritable and tended to lie in the prone position with his legs curled under him and his eyes turned away from the light He had a cold pinkness of his extremities, a mild desquamating rash over the lower part of his trunk, and an angular stomatitis His pulse-rate was 120 and his blood-pressure 130/90 mm Hg Examination of the central nervous system revealed no localising abnormality, he could see and hear well, but his mental state was obviously retarded for a child of $2^{1}/_{2}$ years Investigations included chest and skull X-rays, electroencephalography, serum-calcium, phosphorus, urea and sugar, urine for abnormal metabolites, Wassermann reaction, and blood-count, which were all essentially normal, but the erythrocyte-sedimentation rate was 40 mm in one hour, and a twenty-four-hour specimen of urine showed an excretion of 207 μg of mercury

A further history taken from the parents at this stage did not reveal any access to mercury from any of the usual sources, but on close questioning it was discovered that just before the onset of the fits the lawn had been dressed with lawn sand The weather had been fine at this time and it was some four days before rain washed the sand into the earth. In the meantime the child had been playing on the lawn most of each day The child was not seen to eat the sand, but later in the ward he showed the usual tendency of his age to put everything in his mouth A specimen of this lawn sand was found to contain about 1 part in 50,000 of mercury

The child's subsequent progress was slow but uneventful He remained irritable for some days and showed a tendency to an inverted sleep rhythm with wakefulness at night and drowsiness in the day Before discharge the urinary mercury excretion was 17 μg in twenty-four hours

When last seen in June his good progress had been maintained, though he was backward in his speaking and had had two short episodes of urticaria

Mercurised lawn sand is a dressing applied to lawns to kill unwanted moss Its use is quite extensive in this country The possibility of absorption of mercury from this source has not, to my knowledge, been recognised and I hope this case will draw attention to the fact

I should like to thank Dr Wilfrid Sheldon for permission to report this case and for his help and advice in the preparation of the text

Evelina Children's Hospital,
London, S.E.1
J W SCOPES

LECTURES ON TAPE

SIR,—I have just read your note[1] about the suggestion of Graves and Graves[2] that there should be a central library of tape-recordings and a collection of machines for hire

Each month about 30,000 American and 1000 Canadian doctors are doing just what this note suggests—i e., keeping up with advances in medicine and surgery by listening to tape-recordings prepared by our organisation.

The Audio-Digest Foundation (a non-profit subsidiary of the California Medical Association, whose excess reserve funds are contributed to America's 79 medical schools) issues 5 different series of programmes Subscribers to surgery, internal medicine, obstetrics-gynæcology, and pædiatric programmes receive a new hour-long tape every two weeks, those in general practice receive new programmes each week

The tape-recordings themselves survey the current world literature and provide the rural practitioner with expert scientific lectures by leaders in world medicine Each programme contains at least 2 fifteen-minute lectures by an expert in his chosen specialty

I write to let your readers know how many of their American and Canadian colleagues are keeping up with medical advances, and to suggest that these tapes (with appropriate equipment) might be set up in central locations throughout the British Isles for the use of interested doctors

In America the annual subscription to the specialties is \$81 50, and for the weekly general-practice series it is \$162 At present, customs and excise difficulties prevent the importation of our programmes into England, but with enough interest from the British medical profession it is possible that these obstacles might be overcome

1919, Wilshire Boulevard,
Los Angeles, 57, California.
CLARON L OAKLEY
Editor, Audio-Digest Foundation.

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[1] *Lancet*, 1957, ii, 1346

[2] Graves J C., Graves, V *Research Newsletter*, College of General Practitioners, 1957, 4, 325

BIOCHEMICAL CONCEPTS OF SCHIZOPHRENIA

SIR,—Dr Smythies, in his interesting review (Aug 9), refers to the observations of Örstrom and Skaug[1] upon adenosine triphosphate (A T P) turnover by the blood cells of schizophrenic patients So far as is known no report has appeared since 1951[2] which bears upon these findings We have found no differences in the rates at which ^{32}P, added to whole blood incubated at 37°C for 60 minutes, is incorporated in the A T P, inorganic phosphate, 2 3-diphosphoglycerate, and hexose monophosphate fractions of six female psychiatric patients (aged between 18 and 35, three of whom were suffering from schizoid disorders and three from neurotic disturbances) The uptake by the cells of all six subjects are within ± 1 standard deviation of the mean values obtained on 6 separate observations with the blood of five normal subjects in this laboratory Neither was there any difference in the phosphate content of the fractions examined

Department of Pharmacology,
London Hospital Medical College,
London, E 1

J L H LAITY

DEATH OF A BOXER

SIR,—A number of physicians have written that in long associations with both amateur and professional boxing they cannot recall any cases of cerebral injury Having examined many boxers over many years, I have seen numerous cases of cerebral and other injuries in amateur and professional boxers and reported them in detail In this letter I shall confine myself to a few selected references

In 1942 I described[3] a young amateur boxer who died as a result of a blow to the jaw The fight was held under the supervision of the appropriate boxing authorities Necropsy revealed a laceration of the left temporal lobe and an extensive intracranial hæmorrhage

In 1947 I reported[4] the death of a 23-year-old professional boxer who " participated in a public fight under the auspices of the Board of Control for Professional Boxing and Wrestling ", with a medical officer in attendance He was knocked out and remained unconscious for several days An emergency operation was performed and a right-sided subdural hæmorrhage drained The patient died a fortnight later, postmortem examination revealing some old blood clot adhering to the inner surface of the dura mater, and purulent meningitis

In 1956 I mentioned[5] 2 cases of boxing injuries to the mid-brain, one concerning a young man who died on the 21st day after a fight in which he was knocked unconscious At necropsy tissue softening throughout the brain-stem was found The other case was that of a 24-year-old boxer who had been in the ring for many years and who, following a fight, suddenly noticed tremor of the left hand which rapidly spread towards arm, shoulder, and head, leading within a short time to the development of a typical parkinsonian picture

In 1948 I detailed[6] 10 cases of boxing injuries to the eyes in previously healthy men, among them tears in the iris with hyphæma, cyclodialysis, traumatic choroiditis followed by detachment of the retina, choroidal tears near the fundus, hæmorrhages in the vitreous body, widespread macular changes, and rupture of the lamina elastica posterior These findings were subsequently corroborated by Doggart[7]

In 1944 I told[8] the story of the fatal collapse of a boy, aged 10, after a regulation boxing fight, necropsy revealing an organised occluding thrombus in the coronary artery There were fresh extravasations of erythrocytes between intima and media around the occluded area The latter had, I think, been caused by the blows received during the boxing fight and initiated the chain reaction which led to the child's death

In 1950 you published[9] an editorial which I felt summed up the argument In 1956 I made a comprehensive review[10] of the evidence as it was then available in the literature

In case it should be argued that the percentage incidence of boxing injuries is small, I refer to two competent electro-encephalographic studies on amateur boxers[11, 12] The implications of these two investigations are truly devastating in that they prove a much greater vulnerability of the brain to the kind of blunt traumata that are common in boxing than had previously been suspected

The medical facts about boxing are no longer in question But it is certainly a problem of far-reaching psychological and moral significance that issues like this which call for radical social action on the part of our profession, still find vociferous defenders

University of Kentucky,
Lexington, Kentucky

ERNST JOKL

SURGERY FOR PULMONARY TUBERCULOSIS

SIR,—I am very interested to read in your report of the conference on chest diseases (July 19, p 142) that the therapeutic compass is pointing away from surgery in pulmonary tuberculosis That, in my view, is not necessarily so for the patient whose career is an arduous one and who wishes to pursue it (for example, the fighting soldier) or who wishes to emigrate to a country with stringent rules barring tuberculous subjects

Admittedly there is normally no case for resection, in suitably localised reversible disease, in the absence of drug resistance In the past non-cavitated apparently solid disease, thought to be irreversible, may have been resected because it was not appreciated that some such lesions may show almost complete radiological resolution after 12 months or more of chemotherapy

In the first 75 Gurkha patients with tuberculosis on long-term chemotherapy who were referred by me from Malaya for partial lung resection in the Army Chest Centre, 8 (10 6%) were removed from the surgical list after the following periods of chemotherapy (months) 23, 23, 21, 21, 17, 16, 15, and 12 The unusual drug regime used was streptomycin (1 g daily) and isoniazid (2 × 100 mg daily) for at least 30 days Thereafter, both drugs in the doses stated were given together on the same day every second day[13, 14] Radiological resolution proceeded so far that surgery was no longer considered necessary The proportion of withdrawals is less than some surgeons experienced in the days of long surgical waiting-lists and when long-term preoperative chemotherapy was the exception in this country

It is not disputed that with long-term chemotherapy, in the absence of emergence of resistant strains of *Mycobacterium tuberculosis*, bacteriological examination of apparently irreversible lesions shows a progressively high sterilisation-rate of such lesions the longer the preoperative course of chemotherapy Nevertheless in my opinion this must not give cause for complacency, especially when young people are treated with long-term chemotherapy alone, particularly when we consider the increased, almost alarming, rate of notifications in the older age-groups, indicating the resurgence of active tuberculosis in the vicinity of pulmonary lesions formerly considered quiescent or healed

There is, of course, a case for not advising surgery for patients on long-term chemotherapy in the absence of resistant strains, for there is presumptive evidence that *Myco tuberculosis* will be exterminated in most, if not all, lesions

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[1] Örström, A Skaug, O *Acta psychiat ,Kbh* 1950, 25, 437
[2] Örstrom, A *Arch Biochem* 1951, 33, 484
[3] *Lancet*, 1942, i, 603
[4] *ibid* 1947, i, 888
[5] *Trans Amer neurol Ass* 1956, p 125
[6] *Arch Ophthal* , N Y 1948, 39, 643
[7] *ibid* 1955 54 161
[8] *Lancet*, 1944, ii, 659
[9] *ibid* 1950, 1006
[10] *Zbl Neurochir* 1956, 16, 28
[11] Larsson, L E , Melin, K A , Nordstrom Ohrberg G , Silfverskiold, B P , Ohrberg, K *Acta psychiat ,Kbh* 1954, suppl 95
[12] Pampus, F , Grote W *Arch psychiat* 1956, 194, 152
[13] Mackay-Dick, J , Rothnie, N G *Tubercle*, 1954, 35, 182
[14] Mackay-Dick, J , Slattery, D A D *Brit med J* 1958, i, 888

Nevertheless, the patient should also be informed of the excellent results of resection in suitably localised irreversible disease in these days of skilled thoracic surgery, negligible operative mortality-rate, and slight incidence of complications As your report rightly says, not only the age and sex of the patient but the extent, irreversible character, and destructiveness of the disease must be considered To that must be added the patient's career, with particular reference to careers involving severe strain and possible emigration

In certain countries evidence of tuberculosis of the lungs bars acceptance of potential immigrants The reaction of such authorities to the applicant with radiological evidence of pulmonary tuberculosis, no matter the duration of successful long-term chemotherapy and however fit and bacteriologically negative he may be, can be well imagined

It seems there will always be absolute indications for resection in pulmonary tuberculosis—e g , destroyed lung, bronchostenosis, bronchiectasis, rigid cavities, &c) It is my belief that the case for resection is as strong as ever, the only difference being that the time for surgery in many of the specially selected cases may be much later than formerly This aspect of the case for surgery should be represented to the patient with the same skill as the opposite view and with special reference to his future career After all it is the patient with whom the final decision should rest Failure to give him an impartial briefing on both sides of the question of long-term chemotherapy with or without resection means that the pendulum is swinging into the dark and the compass bearing is not reliable

Army Chest Centre,
Hindhead, Surrey

JOHN MACKAY-DICK

FAILURE OF DETERGENTS TO DISINFECT

SIR,—We were most interested in your annotation of Aug 9 regarding " failure of detergents to disinfect "

There is, of course, evidence to support the claim that quaternary ammonium compounds show greater activity against gram-positive than gram-negative organisms, and it is also true that *Pseudomonas pyocyanea* seems to be one of the most resistant organisms, but at the same time the evidence does indicate that, in the dilutions recommended for ' Zephiran ', even *Ps pyocyanea* should be killed within ten minutes That this is so is also pointed out by Plotkin and Austrian [1] whom you quoted They reported 40 cases of bacteræmia (not septicæmia) due to *Ps pyocyanea*, the result of unsatisfactory skin disinfection using swabs saturated in a 0 1% solution of zephiran It was pointed out that all of them were due to this organism growing in a solution of zephiran from which most of the quaternary had been adsorbed into swabs stored in it so that the concentration of the solution was lowered to an ineffectual level They emphasise " the potential hazard of infection from the improper use of such solutions " We are therefore dealing with errors of technique rather than the ineffectiveness of the disinfecting agent

I believe that in this country quaternary ammonium compounds are frequently used for the sterilisation of heart-lung machines and up to the present this appears to have proved completely successful Again, this seems to suggest that matters of technique might have been at fault

You mention that quaternary ammonium compounds are not very satisfactory skin disinfectants and for this purpose 2% iodine in 70% spirit is still supreme It is interesting to recall that Gardner [2], while supporting the efficacy of tincture of iodine for skin sterilisation, also concluded that the detergent zephiran in 70% ethyl alcohol gave satisfactory disinfection in 30 to 45 seconds

While fully recognising the problem posed by the difficulty in eliminating *Ps pyocyanea* because it is the most resistant organism to quaternary ammonium disinfectants, it is a rather widespread generalisation to conclude that quaternary ammonium disinfectants are as specific in their action as sulphonamides I feel that the conclusion should be that just as heat sterilisation must be done correctly in order to prevent the innumerable failures that have been observed because of insufficient heating or faulty autoclaves, &c , so similarly the quaternary ammonium compounds must be used with the knowledge of their properties and according to the suggested routines in order for them to prove the effective agents they are

Bayer Products Ltd.,
Kingston-on-Thames,
Surrey

K BOHEIMER
Medical Adviser

DEVELOPMENT OF RESPIRATORS

SIR,—I was very interested to read your leader of Aug 9, in which you attribute priority for the inception of the alligator principle in respirator cabinet design to Both and imply that it was his model which prompted the manufacture of cabinets of this type in the United Kingdom It seems fair to point out that, independently and without any knowledge of Both's alligator model, Capt. G T Smith-Clarke in Coventry in 1952 conceived, designed, and built a quarter-scale model of an alligator respirator—later put into production as the Smith-Clarke cabinet respirator [1, 8]

It was in the following year (1953) that the Ministry of Health bought for trial two of Both's new alligator-type machines [2] Again, in 1952, Captain Smith-Clarke modified (with due regard to the draft performance specification of the Ministry of Health, breathing-machines group) five of the original Nuffield (Both) respirators [3] His pattern of modification was later adopted as the standard scheme for the country at large The items in this modification did not at first include a split-head which was added at a later stage—i e , after Captain Smith-Clarke had already designed his alligator

Whilst on the subject of Captain Smith-Clarke's work it is tempting to recall some of his other contributions to respirator practice in *this* country, such as the ingenious hand-pumping arrangement on the modified Nuffield motor-bellows unit,[3] his infant and child-size cabinet respirators, his adoption of the wrap-over neck collar, his positive-pressure attachment for use when a cabinet is opened,[4] his mechanised inspiratory-expiratory valve and arrangement for optional negative pressure as fitted to his intermittent positive-pressure respirator,[5] his robust and powerful foot sucker,[6] and finally the Smith-Clarke standard testing unit.[7]

The story of these developments is set out in the James Clayton lecture [8] given in 1956

Whitley Hospital, Coventry

J F GALPINE

ULCERATIVE COLITIS

SIR,—Dr Sim and Mr Brooke (July 19) seem to me to misrepresent the current psychosomatic concept of the ætiology of ulcerative colitis Do they really believe that dependable information can be got (*a*) by questionnaire, (*b*) retrospectively, and (*c*) by seeking answers to questions which are not relevant to the psychopathology of the disease—notably the incidence of anxiety and depression ?

I can think of no important contribution to the subject in recent years in which anxiety and depression have been considered paramount in the ætiology Excessive dependence and

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[1] Plotkin S A Austrian, R *Amer J med Sci* 1958, 235, 621
[2] Gardner, A D *Lancet*, 1948, ii 760

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[1] Galpine, J F *Lancet*, 1954, i, 707
[2] Report of the Medical Research Council for the year 1956-57, p 12 H.M Stationery Office.
[3] Smith, R E *Lancet*, 1955, i, 674
[4] Galpine J F *ibid* 1954, i, 1013
[5] Smith-Clarke, G T , Galpine, J F *ibid* 1955, i, 1299
[6] Galpine, J F , Brady, C. *ibid* 1955, ii, 1340
[7] Galpine J F , Smith-Clarke, G T *ibid* 1955 i, 722.
[8] Smith-Clarke, G T Mechanical Breathing Machines James Clayton Lecture, 1956 Institution of Mechanical Engineers

emotional immaturity, extreme sensitivity, inability to cope with real or imagined insults, often verbal, the open expression of anger replaced by a disposition to brooding resentment over periods of weeks, months, or years, are all to be found in these patients, but they are not likely to be uncovered by the methods adopted by Dr Sim and Mr Brooke

I do not understand the importance they attach to which comes first, bleeding or diarrhœa It seems quite irrelevant to the truth or untruth of the psychosomatic concept It probably depends on whether disturbance in mucosal vascularity or motility and secretion predominates, and upon which area of the large gut is mainly affected, and the degree of severity

If, as Dr Sim and Mr Brooke seek to prove, ulcerative colitis is not a psychosomatic disease, how do they account for the accumulating reports, from Holland, U S A , and this country, that psychotherapy is efficacious ?

Ipswich J W PAULLEY

CHRONIC PSYCHONEUROSIS IN GENERAL PRACTICE

SIR,—I enjoyed Dr Watts' readable chatty article in your issue of Aug 16, but I think him unduly pessimistic about the chances of cure One reason for this may be his frequent use of phenobarbitone The barbiturates have an immediate sedative action but this is followed by toxic depressant effects in proportion to the dosage They also render patients less accessible to psychotherapy, particularly re-educational psychotherapy, since they tend to dreaminess and letting the world go by rather than to tackling the causes of basic maladjustments in which the neuroses have their origin

I also think it fatal to give in to a neurotic patient's demand for a placebo A bottle of medicine signifies for him organic, as opposed to neurotic, illness, and an essential step in the treatment of the psychoneurotic is to secure his acceptance of the psychogenic nature of his symptoms—often against strong resistance on his part

Wallasey, Cheshire LENNOX JOHNSTON

COUDÉ STRAIGHTENED OUT

SIR,—In the winter number (vol 4, no 6) of *The Leech*, the journal of the Cardiff Medical Students' Club, there appeared an article on Emile Coudé (1800–70), a surgeon of Niort, France, who, it was alleged, invented, and in 1835 published an account of, the Coudé catheter

This biography was written in a serious and restrained vein, and was replete with two references, one to the autobiography of Emile Coudé, and another to *Le Mois Médical* for a description of the invention In addition, the article contained a reproduction of a woodcut purporting to be a likeness of the inventor

We have been able to prove that the whole of this article is a fabrication, and the references are fictitious To expose this deception is of practical importance As a result of the hoax, a number of pages of the 11th edition of *A Short Practice of Surgery* that were passed for press have had to be reset in so far as the capital C of Coude is concerned, and biographical footnotes to Emile Coude deleted

To save others from falling into this mire, we hope that you will publish this letter The coudé catheter was invented by Louis Mercier (1811–82), the eminent Paris urologist, so well known for his description of the inter-ureteric bar Mercier announced the invention of the coudé catheter in 1836, and of the bi-coudé catheter in 1841 Being translated, coudé (the adjective) means bent, coude (the noun) means elbow

HAMILTON BAILEY

W J BISHOP
Editor, *Medical History*

A CLIFFORD MORSON
President of the Société Internationale d Urologie

Obituary

KENNETH WELDON GOADBY

K B E , M R C S , L D S , D P H

SIR Kenneth Goadby, who died on Aug 10 at Walton-on-the-Hill at the age of 85, was a bacteriologist who practised his specialty in the borderlands of medicine, and he will be remembered for the resource and vigour with which he applied its techniques to the problems of odontology and industrial medicine

Shell

He was born at Gravesend, the son of the Rev J J Goadby, and was educated at the Grammar School, Henley-on-Thames, and at Reading University He began to study dentistry as an apprentice, but an uncle offered him the opportunity to take a dental qualification, and after a course at Guy's Hospital he qualified in 1896 While he was practising as a dental surgeon he went on to take his medical qualification in 1900 and the D P H a year later He was still a student at Guy's when he met J W Washbourn, who first interested him in bacteriological research, and from 1899 to 1902 Goadby spent part of his time working in Washbourn's laboratory at Guy's In 1903 he was awarded the Tomes prize of the Royal College of Surgeons of England

The following year he was appointed lecturer in bacteriology at the National Dental Hospital, and he continued to hold this appointment after the hospital became the dental department of University College Hospital Here he was drawn into the circle of A V Hill, Barcroft, Dale, Adrian, and Walter Fletcher He was later lecturer in oral hygiene at the London School of Hygiene In 1923 he drew together in his *Diseases of the Gums and Oral Mucous Membrane* what he had over the years learnt and thought about oral bacteriology He interpreted his subject generously, and described not only the diseases of the title but also the effect of mouth conditions on general health, with warnings on the bacterial dangers of whole-scale extractions and on the effect of vitamin deficiency on the jaws and gums of infants In an authoritative section on metallic poisoning of the mouth he drew on his wide experience of industrial toxicology, for he had for many years been one of the Home Office's specialist medical referees for industrial poisoning He sat on departmental committees dealing with the phosphorus rules for match factories and the causes of lead poisoning in industrial processes He was a member of the medical advisory committee of the Ministry of Mines During the 1914–18 war he also served on the War Office committee on tetanus and as honorary bacteriologist for vaccine therapy at the Royal Herbert Hospital, Woolwich For this work he was appointed K B E in 1918

Throughout his life he had always been something of a lone wolf, and after the 1914–18 war he devoted himself to private practice But he remained alert to new problems and new interests Towards the end of his life he was active at the meetings of the Physiological Society and he published in 1949, with his son Dr H K Goadby, a paper on the nervous pathway of the psychogalvanic reflex He held his lectureship at U C H till 1947, and, J L D B recalls,

"He was an ever familiar figure at students' society dinners, where he made a point of speaking to all his colleagues and friends Though we saw little of him in later years, he will always be remembered as an enthusiast in his own subject and a great lover of social functions, where he mixed freely with the students"

He was one of the original members of the medical committee of the Scientific Film Association, which was started in 1942, and later became president of the association R Mac K writes

"Sir Kenneth Goadby gave sterling help in promoting the use of films in medicine and health education As chairman from 1947 to 1952 of the medical committee he gave generously of his time, guiding gently, in a most friendly way the enthusiasm, impetuous at times, of his younger colleagues This was after he retired from his hospital work but he always took in new ideas and put the good ones into action When he resigned as president he was made the first (and only) honorary vice-president of the Association"

He married in 1898 Constance Eva Olding, and leaves one son

JOHN JEFFREYS DENNIS

CB, M.D, M Ch Q U Irel

Surgeon Rear-Admiral Dennis died at his home at Beaconsfield on Aug 4, some months after his 100th birthday

He was the son of Paymaster-in-Chief T R Dennis, R N, and he was educated at Mannamead School, Plymouth He studied medicine in Cork and Dublin, and in 1880 he was one of the last graduates of the Queen's University of Ireland (which in that year became the Royal University of Ireland) In 1881 he joined the Royal Navy as a surgeon, and the following year saw service in Egypt and received "an expression of Their Lordships' satisfaction" for his able performance of his duties In 1892 he was promoted staff surgeon, and he was surgeon of H M S *Turquoise* during operations in the Eastern Sudan in 1884–85, when he was awarded the Egyptian medal and the Khedive's bronze star For the next two years he served with the Naval Brigade and he landed with the Army during the Burma Annexation War He was present at the capture of Mandalay and took part in an expedition to Bhamo

In 1896 he was appointed fleet surgeon, and he again saw active service when he was with H M S *Highflyer* during the naval and military operations in Eastern Somaliland from 1902 to 1903 In the course of his African service he qualified as an interpreter in Swahili In 1907 he was promoted deputy inspector-general and six years later surgeon general During the 1914–18 war he was medical officer in charge of the R N Hospital, Haslar, Gosport, and he was appointed C B in 1916 for his work there. He was placed on the retired list in 1918 He was made a commander of the Ordre de la Couronne Belge in 1919

Appointments

Clark, J A L, ch m Edin., f r.c s.e consultant surgeon, Stracathro Hospital, Brechin, Angus
Clarke, Mary D, m b Lond, m r c.p assistant m o, Hertfordshire.
Dick, Sheila M, l.r.c p i assistant m o and school m o, Rothwell division of Yorkshire
Dunn, A S, l.r c.p e, d c.h assistant divisional m.o, Bury (near Manchester) area.
Garfit Clowes, Louise, m.b Belf, d p h assistant m o, Surrey
Kershaw, J B, m.b Lond, d p h m o h, Hinckley and Market Bosworth
Latham, Alice m b, b sc Wales, d obst, d c.h assistant m.o, Surrey
MacIntyre Sheila, m.b Glasg, d p h assistant m o h, Argyllshire
Morgan, T H, m b Cantab, f r c.s consultant in traumatic and orthopaedic surgery, Swindon/Cirencester area hospitals
Mouat, J S V, m b Aberd, d p m assistant psychiatrist (s.h.m o), Prudhoe and Monkton Hospital
Murray, B A, m.b Dubl, d p h assistant divisional m o, Lancaster area
Owen, Kenneth m s Lond, f r c.s surgeon, St Peter s, St Paul s, and St Philip s Hospitals, London
Yealland, M F T, m b Cantab, m.r.c.p part-time consultant neurologist, Addenbrooke s Hospital and regional hospital board hospitals

Notes and News

ON RONGELAP AND AILINGINAE

On March 1, 1954, a thermonuclear device was fired on Bikini atoll in the United States Atomic Energy Commission's Eniwetok Proving Grounds in the Marshall Islands This on-the-ground detonation generated large quantities of radioactive substances, and after the explosion unforeseen wind changes carried these materials in unexpected amounts to inhabited atolls, the nearest of which were Rongelap (about 100 miles distant) and Ailinginae (75 miles) In a lecture at Guy's Hospital last week, Dr Eugene Cronkite, of Brookhaven National Laboratory, New York, described some of the consequences of this accident It is important to realise that this ground burst created a situation which has no close relevance to the question of long-continued worldwide fallout from nuclear weapons fired at a great height

267 persons on four atolls were exposed to this dense local fallout The best estimates of the possible whole-body doses of γ-radiation in air up to the time the atolls were evacuated (between fifty and sixty hours after the explosion) were 175 r on Rongelap and 69 r on Ailinginæ Soft γ- and β-radiation from fallout on the ground and particularly on the skin itself gave a superficial dose high enough to produce skin lesions and epilation These changes were first observed two to three weeks after exposure on skin contaminated by fallout, and the first evidence of damage was increased pigmentation in the form of dark brown to black macules, papules, and raised plaques In about 20% of the people most heavily exposed deeper ulcerating lesions developed, usually on the feet or neck Most of them healed rapidly Regrowth of hair, of normal colour and texture, began about nine weeks after exposure and was complete at six months 23 Japanese fishermen were exposed to the same fallout, and in them the severity and course of the skin lesions seemed to be similar to those observed in the Rongelap Marshallese

Blood changes in those exposed on Rongelap indicated the following course of events [1]

(i) The total white count increased during the first two or more days and then fell below normal The count then fluctuated for some weeks and became stabilised at a low level during the seventh or eighth week About the ninth or tenth week it began to go up again, but complete recovery might take several months or more Neutrophil counts took a parallel course

(ii) The drop in lymphocytes was early and profound and the count may not return to normal for months or years

(iii) The platelet count fell regularly, reaching a minimum on the thirtieth day Some recovery was evident early, but it might not be complete several months after exposure Dr Cronkite said that platelets might drop as low as 25,000 per c.mm before bleeding began as the result of irradiation

The depression of peripheral cellular elements in the blood suggested that exposure on Rongelap was moderately severe, probably within 50 to 100 r of the level where some fatalities would have resulted.

Speaking of the treatment of persons exposed to high doses of total-body γ-radiation, Dr Cronkite observed that transfusion might be more hazardous than radiation The Japanese fishermen had been vigorously transfused, and serum hepatitis might have done some of them more harm than they would otherwise have suffered Only when doses were thought to be in the uniformly lethal range would he advise active treatment, such as transplantation of bone-marrow Otherwise the patient should be observed and conditions treated as they arose

OSTEOPATHY

The origin and development of osteopathy in Great Britain are described in *The Osteopathic Blue Book*,[2] which is claimed to be the first authoritative account of its sort One of the main aims of those who produced this book was to enable the public to differentiate between osteopaths who have been trained as such and those who have not

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[1] Some Effects of Ionizing Radiation on Human Beings U S Atomic Energy Commission, July, 1956

[2] Compiled and issued by the General Council and Register of Osteopaths Ltd, 16, Buckingham Gate, London, S W 1 Pp 78

RISING COSTS AND DIVIDED RESPONSIBILITIES

The development scheme at the Radcliffe Infirmary, Oxford, continues to incur authoritative displeasure At the beginning of this year the Comptroller and Auditor General, criticising it under a transparent veil of anonymity, pointed out that the original estimate of £434,390, made in 1955, had been allowed to grow to £1 million, and that a considerable amount of work had been started "without the Ministry's prior authority"[1] The Ministry of Health, though not defending the methods of the board of governors of the United Oxford Hospitals, have admitted that they are satisfied that the scheme will not cost substantially more than if a more orthodox procedure had been followed But the Committee of Public Accounts[2] now challenge this Ministerial clemency, and firmly state that they have no doubt that "substantial economies could have resulted had the work been properly planned in advance and had the various additions requested during the course of the work been critically examined by the Ministry and the Treasury before being put in hand" The "unenlightened rush" which had taken the place of advance planning and critical examination of the work in process must, in the committee's view, account for part of the increased cost

Putting aside the debatable question as to whether the extra expenditure was avoidable, the committee is concerned that the board should have been able "under extreme pressure by the University" to commit the Ministry to expenditure which had not been approved Though the primary responsibility for these irregularities must rest with the board, the committee tax the Ministry with ineffective supervision which had "considerably weakened Treasury control over the expenditure" They ask for a review of the Ministry's arrangements for financial control of large building projects and suggest that this is especially necessary where responsibility is divided between a board and a university

The Ministry has already recognised the importance of adjusting the balance of financial responsibility between hospital and academic principals, and, with the Treasury and the University Grants Committee, have devised a formula[3] defining in principle what a university's contribution should be towards the cost of a building to be shared with a teaching hospital This formula had not been agreed when the original arrangements for the Oxford scheme were made The University of Oxford's promised contribution to a total which was then £434,390, was £170,500, with a further £31,500 towards equipment The Ministry consider that the part of this contribution (£138,500) allocated to the work that has already been done is not less than the university's contribution should be under the formula, but the proposed contribution towards the remaining work and towards equipment is much less than it would be under the formula The university is unable to find more money, and in the circumstances the Ministry, in consultation with the Treasury and the U G C, have agreed not to seek a further contribution The whole of the expenditure will therefore have to be met from the Vote for the National Health Service and will reduce the amount available for capital expenditure for the service The committee feel that this is an improper use of moneys voted for the health service, and they recommend that in future commitments to provide facilities and equipment which are not strictly an N H S liability should not be made until money is available to meet them from sources other than the Health Service Vote

University of Cambridge

On Aug 2 and 5 the following degrees were conferred

M D—F Ashton, A L T Easton, P M O Massey, George Meachim, •Vishnu Sarma, Leonard Weiss

M B, B Chir—•I F M Buchanan, R C L Feneley, •J G Lancaster

M B—•P J Ball, D A Birkett, •Shirley A Bolt, •E F Brooks, F T Brough, Jan Chippendale, G M Davies, •Nerys Davies, •A J Earl, Audrey E Fairey, A F Fleming, John Hedley-Whyte, N E S Holden, •I D Hunter Craig, R H Johnson N W Oakley, •Allan Reynolds, •Heather M Rumsey, •W G Shakespeare, •Margaret R Skelton, A C Smith, G C Sutton, J C Twomey, H B Valman, D M Whiteford

• By proxy

Royal College of Obstetricians and Gynæcologists

On Friday, Sept 26, at 5 P M at 1, Wimpole Street, London, W 1, Mr V B Green-Armytage will give the Green-Armytage Anglo-American sterility lecture His subject will be recent advances in the surgery of infertility Tickets may be had from the secretary at the college, 58, Queen Anne Street, W 1

Royal Society of Medicine

Anæsthetic section—This section is offering a prize (£30) for the best paper submitted by a senior registrar or registrar holding a clinical appointment in an anæsthetic department or hospital

Fellowship of the society is not necessary for entry The subject will be of the author's choice but must be connected with anæsthesia All papers must be submitted by Jan 1 Further details can be had from the hon secretary of the section, 1, Wimpole Street, London, W 1

British Medical Association

This Association is offering the following essay prizes

A Sir Charles Hastings prize (£75) and a Charles Oliver prize (£50), open to members who are in general practice, a provisionally registered practitioners' prize (£50), and a medical students' prize (£25)

Further particulars may be had from the secretary, B M A House, Tavistock Square, London, W 1

Freud Centenary Fund

The trustees of this Fund are prepared to give financial support to a small number of applicants who have been accepted, or are eligible, for training at the Institute of Psycho-Analysis in London

This support may take the form of a loan (repayable without interest) or of a grant to cover all or part of the training expenses, and the trustees may grant additional funds in cases of exceptional promise All inquiries should be addressed to the hon secretary of the Fund, 20, Maresfield Gardens, N W 3

Darwinism and the Study of Society

To mark the centenary of *The Origin of Species*, a conference on this subject will be held in Adam House, Edinburgh, from April 8 to 10 Further particulars may be had from Dr M P Banton, 39, George Square, Edinburgh, 8

Pneumoconiosis and Byssinosis Benefit Scheme

Widows and other dependants claiming the death benefit of up to £300 provided under this scheme have been given rights of appeal against an unfavourable decision as to the cause of death (S I 1958 no 1240) Up to now the medical decision on a claim for death benefit has been final

Society for the Study of Fertility

The annual conference of this society will be held next year on May 28, 29, 30 in Dublin

On Sunday, Sept 7, at 10 15 A M, at University College Hospital, London, W C 1, Mr G L Bunton will give a clinical demonstration for general practitioners on cases suitable for pædiatric surgery

The *Medical Electronics Center of the Rockefeller* Institute has prepared a *Bibliography on Medical Electronics*, which has been published by the Professional Group on Medical Electronics, Institute of Radio Engineers, 1, East 79th Street, New York 21

A pamphlet entitled Smallpox and Vaccination, which answers in simple language questions that may be asked by the lay public, has been issued by the Research Defence Society, 11, Chandos Street, Cavendish Square, London, W 1 (*6d*, post free)

The St Thomas's Hospital old students' dinner will be held at the Savoy Hotel, London, W C 2, on Friday, Oct 31, at 7 30 P M Prof O L V S De Wesselow will be in the chair Tickets (£2 2*s*) may be had from the hon secretaries at the medical school

CORRIGENDUM "*Calling Dr Kildare*—In the article by Mr H C Elliot and Dr J M A Lenihan (*Lancet*, 1958, i, 1329) the table should have shown under 'Selectacall' the nature of the signal as buzzer, and speech signal when receiver, with speech button pressed, is held to the ear

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[1] See *Lancet*, 1958, i, 303

[2] H M Stationery Office 1958 *Pp* 32 1*s* 6*d*

[3] See *Lancet*, 1957, ii, 498

The Lancet · Saturday 30 August 1958

THE FRONTIERS OF MEDICINE*

C H STUART-HARRIS
M D Lond , F R C P
PROFESSOR OF MEDICINE IN THE UNIVERSITY OF SHEFFIELD

TWENTY-FIVE years ago the newly qualified graduate in medicine was aware of a sense of excitement and of promise in his future medical career He was about to practise in a world engulfed in one of the great periods of change in its history The world was shrinking, distance was being almost annihilated by the aeroplane, and changes were on foot in the lives of continents, such as Asia and Africa, exceeding those in centuries past Since then there have come the doubtful blessing of television, the surge of power from nuclear fission and thermonuclear reactions, and now the earth satellites, which have caught the popular imagination as almost no other achievement has done

All these are the material consequences of the advance of science But what disasters has mankind not brought upon itself in the same period? We have passed through the most devastating of all wars We exist in a world divided into two political and economic systems Every year we witness new pathetic streams of refugees fleeing from political injustice, and we have knowledge of determined efforts at the enslavement of the mind, and of cruelty which has been unparalleled since the Middle Ages We are told that this is an age of violence

While all these vast changes have been taking place, medicine also has undergone a revolution Dr Barry Wood (1952) described the present phase of increase in knowledge as analogous to the logarithmic phase of growth of a bacterial culture We see daily the miracle of chemotherapy and the triumphs of surgery helped enormously by the advances in anæsthesia There have been a steep fall in the infantile death-rate and a corresponding increase in the expectation of life Some diseases have well-nigh disappeared, at least in Britain, and the pattern of others has altered for the better Moreover new drugs have poured forth in ever-increasing numbers, with the result that the doctor can now treat many conditions which he could not previously Those diseases which cannot be cured can often be endured, though at the expense of much medical care and skill

What are the effects of these changes in the structure of medicine on the future practice of our art and science? What will medicine be like in the future for those of you who now stand palpitating on the threshold of your career? Are the next twenty-five years going to be as changeful and as exciting as those which we have just passed through? I cannot claim to be a prophet but I am willing to look with you into the future

To look at the present frontiers of medicine it is necessary first to look backward, because the frontiers of today are not the same as the frontiers of yesterday When I was a student, it was common to feel that patients were admitted to the medical wards to lie and rot The great watch-word was "masterly inactivity", and many were attracted by surgery because of its comparative air of activity and of its desire to thrust forward Yet it is medicine which has undergone the greater change Today the atmosphere of the medical wards has changed We are in the grip of a revolution in therapeutics For the polypharmacy of yore, with its emphasis on mixtures and nostra, has been substituted by a battery of active remedies—antibiotics, antispasmodics, hypotensive drugs, and steroids—so much so that I sometimes feel that it is my job to go round the ward taking patients off, rather than to prescribe, the various medicines which pour into their mouths, their veins, and their buttocks For these new magical remedies differ from the old in one important particular the old remedies were at least inert and did not therefore harm though they did little good, but the new ones are powerful drugs with powerful actions and must be used with discrimination lest the patient suffer rather than benefit

Therapeutics is not, however, the only branch of medicine to undergo a change The investigation of patients has also become increasingly complex Electroencephalography, refined radiological techniques, cardiac catheterisation, tagging with radioactive isotopes, and many other biochemical applications have become routine modes of inquiry Many of these have stemmed from research, particularly from that discipline which we term clinical science and which can broadly be defined as the application of the experimental method to the study of human illness Moreoever there is no sign that we have yet reached the limit of this press and surge of inquiry However disconcerting it may be to those of us who practise the clinical art, the laboratory is firmly established as the partner of the clinician He, poor fellow, must learn to cultivate the chilly discipline of the laboratory bench, because the days of the clinician's flirtation with laboratory techniques are at an end for him If he does not beware, he will have to accept the technician's results without question.

With this increase in the tempo of medicine we sometimes do not wonder at our new powers Particularly is this true for those of you who are growing up with modern medicine and accept the situation without question Let us pause to seek some reasons for this revolution in medicine It is easy to see that the former frontiers of knowledge have often been thrust forwards by the development of new ideas or from a new approach Often this has happened when the barriers to progress appeared impregnable, and yet in an astonishingly small time they have been reduced

Breaking Through the Barrier

Nowadays we are told by press, radio, and television of the great achievements of so-called pure science The phrase has been coined of a "break-through" One even hears it said that the break-through took place on a particular date, a moment of history, when some miracle was first observed in the laboratory Well, why should we not adopt the same expression in medicine? There have certainly been some impressive break-throughs in medicine in the past half-century

One was when Whipple fed his anæmic dogs with liver instead of ordinary meat and noticed that their blood regenerated more rapidly than he expected From such a chance observation came the liver treatment of pernicious anæmia, which in the past twenty-five years has led to the identification of vitamin B_{12} and has banished mortality from pernicious anæmia

Another break-through was when Fleming saw the tell-tale ring of inhibited culture on the crowded agar plate around the focus of fungal growth from a chance spore of

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* Presidential address to the Sheffield University Medical Society on March 6, 1958.

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penicillium which had flown in through the window That break-through took many years to develop Penicillin, when I qualified, was just a laboratory tool to enable one to suppress unwanted bacteria in a culture so that one could obtain a pure growth of an organism not affected by the substance In its impure state penicillin was extremely toxic and so could not be used therapeutically Perhaps, without the genius of Florey and the chemical knowledge of Chain, penicillin would never have been purified, and thus its priceless benefit would have been withheld from mankind But the break-through *was* pressed home A new form of chemical engineering was born to mass-produce the fungal culture and to purify its product to the present crystals, with the results now known to you all

Serendipity

How did these break-throughs happen? Many think that they were the result of a logical sequence of thought and of work Unfortunately the answer both for these discoveries and for others of their kind is that they seem rather to have been the result of an accident or of chance The realisation that chance plays a dominant role in scientific discovery has been much commented on Cannon (1945) has revived the use of an ancient word to describe it The word is "serendipity", which was used by Horace Walpole in 1754 after reading a fairy-tale entitled *The Three Princes of Serendip* (Serendip was an ancient name for Ceylon) The princes (so Walpole wrote) "were always making discoveries, by accident or sagacity, of things which they were not in quest of"

I tried out this word "serendipity" on one of my clever young men, but he got no further than suggesting that it was a name for a new tranquilliser Far from producing serenity of mind, however, serendipity (in the sense in which Cannon uses it) has an effect better described as galvanic Indeed Cannon illustrates serendipity by the experience of Galvani, who first observed that frogs' legs hanging by a copper wire from an iron balustrade twitched when swung by the wind so that they touched the iron From this simple beginning has come the magnificent growth of electricity which now plays so large a part in all our lives

Another example of serendipity was the discovery of insulin, which came from the accidental finding by Von Mehring and Minkowski that the urine from pancreatectomised dogs was attracting a swarm of flies This phenomenon of experimental glycosuria furnished Banting and his student Best with the idea that the pancreas somehow held the key to human diabetes

Then there was Pasteur's finding that fowls inoculated with an old culture of bacteria causing chicken cholera became ill but did not die, whereas fresh cultures of the same organisms were extremely virulent and caused fatal disease This led him to work on the deliberate attenuation of cultures so as to obtain an avirulent culture or vaccine which could protect against the actual disease Then came the classical experiments on vaccination of sheep against anthrax and Pasteur's work on rabies Pasteur described serendipity in the words "chance favours the prepared mind" Thus many may witness the phenomenon, but only those with the ability to grasp its meaning understand what they see

Of course, it would be foolish to overlook the fact that much scientific research consists of hard slogging on a planned basis in which chance plays very little part, but we have to draw a distinction between research and discovery The first step towards a real discovery may have been taken either as a result of intuition based on observation or because of an experiment which was planned answer one question but showed something else Jenn is said to have been startled into work on smallpox by th remark of a pretty milkmaid that she would never ta smallpox because she had had cowpox Perhaps, howev Jenner would never have been successful in his work b for John Hunter's advice "Don't *think*, try"

In virus work it has been the advice to try which seen to have yielded discoveries, but pure chance has al played a role at times When Wilson Smith, who lat became professor of bacteriology in Sheffield and now University College Hospital, had exhausted the vario animal species available for experimental work o influenza in 1932, it was Douglas who said "Why n try a ferret?" Thus it was found that the ferret wa susceptible to influenza virus, and this discovery opene up a huge new field in virology Contrast this with th story of Richard Shope, who injected some of his favouri laboratory animals, pigs, with swine-influenza bacilli ju before going away for a holiday A few days later h received a telegram from his technician "Hogs hav swine 'flu" This ended his holiday but began the wor on the strange story of the earthworm reservoir o pig-influenza virus

Again the result of "trying the impossible" ha brought a rich reward in work on polio John Enders an his team at the Boston Children's Hospital in 194 attempted the impossible by inoculating some poliovir into test-tube cultures of human fibroblasts Poliomyeli virus was so highly specific for the nervous system, sai the pundits, that it would grow in none but the mos highly differentiated of all mammalian cells—the nerve cell—and here were our experimenters casually implantin it into the lowliest of all cells—the fibroblast, which grow like a weed in the garden of a tissue-culture and outstrip and chokes the growth of other cells The fibroblasts thu inoculated succumbed to the virus—they withered and died Poliovirus had been grown in a test-tube and in a quantity far exceeding that previously found in the inoculated monkey This discovery opened the door to much further work on the best tissue-culture cells to use for the preparation of a human vaccine When monkey renal epithelial cells were chosen as the best available medium, Salk applied himself to the inactivation of the virus in the culture and eventually selected formalin as the most appropriate chemical for killing the virus and thereby rendering the vaccine safe

The Follow-through of Enders' Discovery

The story of the Salk vaccine has been told by many people in many different journals It is an astonishing story of success and disaster It is compounded of a mixture of courage, audacity, timidity, and sheer bungling The trials of the vaccine held in the U S A in 1954 exemplified the best tradition of impeccable scientific investigation It was the largest vaccine trial in history Nothing which has happened since 1955 should detract from the greatness of the American achievement For one thing, it required extreme courage to carry out this first trial The child is glorified in America as the most precious form of life I do not believe that Americans are more willing to allow their children to be the subjects of an experiment than we are Yet the child *had* to be the guineapig in this trial of protection, and Americans did not shrink from allowing their children to be inoculated, and they were also willing to allow some of them to act as controls and to be inoculated with a fluid containing

, at all The result justified their faith in their s, and the Salk vaccine was proved to be effective came the Cutter disaster, when certain batches of containing residual live virus caused poliomyelitis . of those who were inoculated and even in their contacts The Cutter disaster was not due to tence on the part of the manufacturers Rather n illustration of the old adage " more haste, less

Had more time been devoted to the methods of the vaccine for live virus and to a proper system of checking the safety tests themselves, it might not ppened At any rate, we in this country felt the tional impact of the disaster, so the British vaccine dified to increase the factors of safety This could eant that our vaccine, though safe, had been robbed tivity, and thus came the need to test its protection trolled trial was thought possible in Britain, but we cceed in measuring the effects of the first few d litres of British vaccine Because there was not vaccine available for all the children whose parents ered, a random selection of the children to be ted was arranged according to their date of birth who were uninoculated furnished a control group subsequent experience of poliomyelitis was the ound to that of the inoculated children The result l that the British vaccine was at least as protective ish children as was the Salk vaccine in the U S A al Research Council 1957)

cannot yet tell how successful the introduction of ccine against poliomyelitis will be in enabling us to l the disease The indications from Denmark, lia, Canada, and the U S A are that it will reduce ssively the yearly attack on our young children. ately we may succeed in banishing poliomyelitis as diphtheria has been banished Imagine the ations of this on the work of doctors in infectious-e hospitals, our colleagues in orthopædics, the therapists, and all those now concerned in com- g poliomyelitis

Medicine and Society

oking back on the past few years I am chiefly ssed by the way in which the trials showed the ged relation between people and doctors In the A poliomyelitis has been a much greater scourge in Britain, its people have contributed millions of s to aid research, and at times it has been the energy he effort of lay people which have created the condi- for an advance in knowledge At times also the rs must have felt as though they were being forced ctivity by a public pressure and conscience which did not share Even in Britain, where poliomyelitis een much less of a menace, the research on the ne has roused much public interest In many other also public interest has grown to the extent that we have to maintain good public relations if only to e that we have the right conditions for our work sometimes means that the scientist has to endure dragged out of his quiet laboratory to provide ers to questions of public interest There has to be k a nice balance between educating the public and g false hopes or fears Some, including many ent doctors, feel that it is not part of the profession's nsibility to educate the public. They go on the iple that " a little learning is a dangerous thing ", that it is far better for people not to know anything t disease or about the symptoms of illness than just a smattering I think this view ignores an important aspect of the times in which we live, which has resulted from the growth of the communication of ideas

Sir Francis Fraser (1958) emphasises that one great consequence arising from the advances in science and technology is our increased ability to communicate with each other Events in distant lands are photographed and viewed in our own homes within a matter of hours We are no longer restricted in our interests to what goes on in our family or social group As a result there is a growing interest in and demand for information on all aspects of our life, including illness Doctors can no longer stand aside and maintain the attitude that it will do no good for the public to know The public *wants* to know, whether it is good for it or not, and it is our new responsibility to provide information which is correct This revolution in the public relations of medicine will certainly affect you in whatever sphere you practise medicine Unless you practise in a mentally defective community, your patients will know more and ask more questions than at any previous phase of our history Your answers will demand great wisdom if the public is not to be turned into a mass of hypochondriacal neurotics

This brings me to the future role of doctors Side by side with the great advances in the technical achievements of our craft we witness a remarkable increase in the public demand for medical care The death-rates go down, but the volume of medical work is steadily increasing Fry (1957), a general practitioner at Beckenham, says that he sees 90% of the patients on his list on one or more occasions in a period of five years Logan and Brooke (1958) find that, at any age and in any month, at least 50% of adults complain of an illness of some kind or another Are these people ill with physical ailments or with neuroses ? The doctors of the Sheffield University Health Service see half of all the students who elect to draw on the University's organisation every year Are students really in need of medical care to this extent ?

One reason for this rising demand to see the doctor is that the many minor ills which befall us all are no longer regarded as inevitable consequences of being alive We all desire not simply life but abundant life, not an absence of disease but a feeling of mental and physical fitness Modern life, with its struggle for existence, its frustration, and its unhappiness, imposes a strain which is too great for the unaided citizen The doctor has become a symbol of society's need for support and consolation Nor is there any sign that this is a temporary phase Modern man, for all his technology, is a frightened creature as much in need of guidance and more in need of faith than his forefathers He is likely to become increasingly dependent on medicine as knowledge advances

Future Conquests

What new Everests of knowledge are there for *you* to scale ? Some diseases have disappeared or are diminishing We can expect, for instance, that diseases such as tuberculosis, now being attacked both prophylactically and therapeutically, will slowly disappear New diseases are appearing—e g , the disorders of the nervous system probably caused by viruses such as the Royal Free disease and aseptic meningitis with a rash New industrial processes—e.g , the use of beryllium for fluorescent strip lights—bring us new hazards A new branch of medicine is growing up to cope with the complexities of the nuclear age, for radiation hazards now exist for the population as a whole and not just for radiologists What new menace exists for man in his attack on outer space can only be surmised But the perils which are endured by Dr Quatermass in his various experiments and which we pass over as the burblings of science fiction may perhaps be taken more seriously if we reflect on the earlier prophecies of Jules Verne and H G Wells The science fiction of one era has been described as the scientific literature of the next So you who will practise medicine twenty years from now may deal with disorders undreamt of today New frontiers will have sprung up as a consequence of man's struggle with his environment

I wonder if you will have learnt the conquest of less romantic evils Will you have taught mankind to prevent cancer of the lung by smoking fewer cigarettes, or will you have rendered the precious weed harmless by removing the carcinogen? I suspect the latter, but I hope you will be more successful in your general task of teaching man to control his habits than we of my generation have been Perhaps at least you will have begun to control disorders such as arteriosclerosis and bronchitis, which may be due in part to our faulty ways of living But will you have found the answer to the riddles of cancer and of the chemotherapy of virus diseases? These subjects appear ripe for the major break-through, perhaps from some entirely unexpected direction Nucleic-acid chemistry is advancing so fast that one wonders about its impact on genetics and on hereditary disease Will you in your lifetime be able to repair the chemical faults underlying so many hereditary conditions? At any rate one can expect an expansion of the frontier which so tightly hems in our power to deal with mental illness Psychiatry has far too long been the Cinderella of medicine, and the next twenty-five years will surely see a revolution here

Finally, may I hope that you will have learnt how to assess the results of your efforts? It is only since the use of clinical trials that we have begun to debunk medicine of much that is false The principle could profitably be extended to include much more than an assessment of a drug or a vaccine The results of surgery and of psychiatric therapy are fit subjects for exploration We must grow in candour as well as in technology

My last remark must be to remind you of the words of the writer of Ecclesiastes (9, 11) which seem a fitting comment on this address

"*The race is not to the swift, nor the battle to the strong, neither yet bread to the wise, nor yet riches to men of understanding, nor yet favour to men of skill, but time and chance happeneth to them all*"

REFERENCES

Cannon, W B (1945) The Way of an Investigator New York.
Fraser, F R (1958) *Lancet*, i, 154
Fry, J (1957) *Brit med J* ii, 1453
Logan, W P D , Brooke, E M (1958) The Survey of Sickness, 1943 to 1952 London
Medical Research Council (1957) *Brit med J* i, 1271
Wood, W B , Jr (1952) *J clin Invest* 31, 611

" We live in a scatterbrained age of distractions Suspended by vague but painful ambition, prodded by anxiety, and baffled by frustration we lose the capacity for sharp and exclusive focus of the attention Attention can be cultivated Don't try several things at once, but whatever you do, take it all in Can you quote a poem exactly, or even the title? The near miss is about as helpful as the telephone number with only one wrong digit Specification, precision, exactness come only with sharp and complete attention "—Prof WILLIAM B BEAN, *The Pharos*, February, 1956, p 13

A NEW MEDICAL CURRICULUM

D C SINCLAIR
M A Oxon , M D St. And
PROFESSOR OF ANATOMY, UNIVERSITY OF WESTERN AUSTRALIA

GRUMBLING at institutions is an ancient sport, and in British medical schools the curriculum is the traditional target for abuse Like the Walrus and the Carpenter, most medical teachers weep like anything to see such quantities of unsatisfactory material "if this were only cleared away", they say, "it *would* be grand" Unfortunately it is not very easy to clear away established curricula which have been moulded by years of gradual evolution Just as nothing is more permanent than a temporary building, curricular material may obstinately persist long after it has outlived its usefulness

Until last year there has also been another hindrance to reform of the curriculum, for the General Medical Council made detailed "recommendations" to the medical schools, specifying a virtually stereotyped course of instruction If the prescription was faithfully followed recognition of the schools was automatic, if not, the issue was clouded with doubt In the circumstances few medical schools felt bold enough to adventure very far away from the well-beaten path

But in 1957 the Council decided that an undiluted and universal orthodoxy might not be a wholly good thing, and, by suppressing the details which used to surround its recommendations, left the way clear for experiments By pure chance it was also in 1957 that the newest medical school in the British Commonwealth opened its doors to medical students Those who had to frame the medical curriculum in the University of Western Australia were thus given a relatively free hand, the bonds of official regulation had just been loosened, and there was no need to dismantle an existing curriculum the components of which had become rusted in position

It is of course true that even in such a promising combination of circumstances it is impossible to plan a curriculum without making concessions to the realities of the local situation The ideal is unattainable, and indeed exists only in the abstract The world is too much with us, late and soon Nevertheless, it may be of interest to examine what has so far been done in Western Australia, and in order to understand the features of the new programme it is necessary to make a brief review of its background

The Background

The University of Western Australia was founded in 1912, and has grown, at first steadily and recently very rapidly, until in 1958 it accepted 2629 matriculated students, including 82 who wished to study medicine The minimum age for entry to any faculty is 17, and, as in other Australian universities, any student capable of matriculating is accepted for tuition in the faculty of his choice For a long time those who wished to become doctors have been able to take the subjects appropriate to the first year of a medical course in Western Australia, but their subsequent instruction has depended on the sympathetic hospitality of other universities—notably the University of Adelaide The increase in population, which has affected Western Australia along with the rest of the Commonwealth, made it more than ever desirable that the State should produce its own doctors, and at the same time the pressure of local applications made it impossible for Adelaide to continue accepting Western Australian students In 1955 an advisory committee suggested that the needs of the State would be met by a medical school with an annual output of 40 graduates (this estimate may require modification later, in the light of future immigration figures) A public appeal was launched for funds, and achieved the astonishing sum of £A570,000 The State Government contributed an additional amount of £A150,000, and undertook to pay the annual costs of the school

The staffing of the new school involved the establishment of nine new professorial chairs within the university All these—anatomy, physiology, biochemistry, pathology, microbiology, medicine, surgery, obstetrics and gynæcology, child health—are now filled, and most of the corresponding junior appointments have also been made The professors of pathology and microbiology are responsible for the corresponding hospital service departments, and the clinical chairs are whole-time appointments, though private consultation work is permitted up to a stipulated maximum each year The preclinical professors have responsibilities in several faculties other than medicine—for example, the department of biochemistry teaches in the faculties of science, dental science, and agriculture, and the department of anatomy is currently dealing with students in the faculties of science, dental science, arts, and education

Eventually it is hoped to establish a medical centre based on a new hospital to be erected close to the university, this is a long-term development, and for the time being the preclinical departments are to be found on the main university site, some four miles from the clinical departments, which are based on the Royal Perth Hospital Teaching in child health and in obstetrics and gynæcology is centred on hospitals about two miles from the main clinical school.

The pattern of medical care in Western Australia is such that relatively few patients are available for teaching purposes, and in any case the Royal Perth Hospital was not constructed as a teaching hospital In consequence there is a limit to the number of students who can be taught from the third year onwards, and this limit is at present set at 48 students in each year The preclinical departments have more accommodation, but, because of their other commitments and their limited staff, only 60 students can be admitted to the second year of the course

By the time the details of the planning came to be considered teaching had already begun at both ends of the curriculum The first students to be dealt with were 16 final-year students who in 1957 returned from Adelaide to finish their course in Perth (and to obtain Adelaide degrees) In 1958 another batch, this time of both final-year and fifth-year students, returned from Adelaide and in addition 60 second-year students began work in the preclinical departments The first Western Australian medical degree will be awarded by the faculty in 1959, but the first students to complete the entire course in Western Australia will not graduate until 1962.

General Planning

This short statement has outlined many of the features of the local situation to which the curriculum had to be adapted For example, complete integration of teaching in the manner of Western Reserve was at once ruled out because the small staffs of the preclinical departments have to meet considerable teaching demands from other faculties, and because the components of the school are geographically dispersed A "self-service" curriculum in the Oxford manner, under the control of tutors, was excluded because of the lack of adequate staff and because of the relative immaturity of the students, most of whom come from schools where there is no equivalent of the British sixth form Any drastic reorientation of the clinical work was initially impossible because of the need to receive back into the fold the Adelaide students who had had an orthodox beginning to their education Examinations could not be held to the minimum demanded by the General Medical Council because of the unrestricted entry to the course, which made it necessary to use the first and second years of the course as a means of student selection And so on, enough has been said to indicate the type of consideration which had to be imposed on the generalised "ideal" curriculum which might possibly have shaped itself in the minds of the faculty

In addition to these local factors, two principles of more general applicability were kept in mind during the planning stage One of these was the value of liaison between the various departments A series of weekly lunch-time meetings was instituted among the professors, and it is proposed to continue this most valuable practice indefinitely Frequent contact and discussion of problems have made it difficult for any department to feel that it has been isolated or unjustly treated, and the sense of cooperation in an important enterprise has not been allowed to die out Each department has gained a most valuable insight into the needs and difficulties of the others, and in this way is undergoing an education which must eventually render it more capable of attempting to educate others

The second principle was that the details of time-table arrangements or teaching methods must never obscure the all-important attitudes of both teachers and taught towards the process of becoming a doctor The human aspect of the curriculum was kept well in front of its mechanical tricks Nevertheless careful consideration was given to the most recent developments in teaching and in curricular reorganisation, and an attempt was made to put into practice the features of these which were best suited to local conditions, although it was fully recognised that what was new and experimental was not necessarily better than that which was old and familiar The details of planning were deliberately kept as flexible as possible, so that modifications could be introduced with little disturbances as they become desirable

Two ideas current in modern medical education were unreservedly accepted by the faculty the first of these was the desirability of allowing the student time to think for himself, and the second was the value of coordination

It was decided that the best way of accomplishing the first objective was to cut down the load of formal lectures as much as possible Part of the time so released has been given over to teaching of the tutorial or seminar type, but most of it has been allotted to the student to use according to his needs In the second and succeeding years of the curriculum one whole day in each week (apart from Saturdays and Sundays) has been left free from organised classes This is naturally strong meat for many students, who have been accustomed at school to have predigested information thrust at them from morning to night, and feel ill-nourished without a steady supply of this homogenised material Accordingly, in the earlier stages of the curriculum "free time" is not quite so free as it is later on, when the student has developed some sort of judgment of his own In the second year, for example, demonstrations, films and talks relating to the subjects being studied are provided These sessions are not compulsory, but are intended to indicate to the student some of the lines along which he could profitably direct his mind Later in the curriculum the students are encouraged to organise for themselves talks from people outside their immediate horizon—a pastoralist, a brewer, an actor, and so on—the idea being to broaden the notoriously limited outlook of a clinical medical student Interspersed with these talks are discussions, some of which are led by members of the department of psychology, and deal with matters such as hypnotism, race and class prejudice, learning theory, and telepathy Students may use their free time to undertake a piece of field work in social medicine, or to visit the families to whom they will be attached as part of their social medicine training

Not only has the student been given time to think, he is actively encouraged to go through this unfamiliar exercise at every possible opportunity For example, many of the practical classes throughout the curriculum have been organised to avoid, so far as possible, the cookery-book atmosphere engendered by following a standard recipe stolidly through to " success " or " failure " Instead, the student is asked to explore the reasons behind the form of the experiments he undertakes, and is asked questions about them which have answers to be found only in his own work and not in any textbook

The concept of coordination between departments has been put into operation at three different stages in the curriculum, and the individual features of these coordinated courses will be described later The first is designed to prevent fragmentation of the preclinical study of human biology into artificially bounded departmental " subjects ", the second aims to bridge the geographical and psychological gap between preclinical work and the study of patients, and the third is an attempt to show how various clinical and preclinical disciplines can cooperate in the solution of problems of preventive and social medicine

There are six years in the medical course In the first two of these the academic terms are of the standard university length—two of nine weeks and one of eight weeks In the third year the first and third medical terms are twelve weeks long, and the second term will correspond to the standard university term, by this means medical students will have the same holiday as the other students, and may thus preserve their connection with university sport and other general university matters as long as possible From the fourth year onwards, however, all the three terms are twelve weeks long and the students move their headquarters to the hospitals

The Curriculum

FIRST YEAR

The cardinal features of the first year are that entry to it is unrestricted, provided the matriculation requirements are satisfied, and that there is at present no exemption from first-year subjects on the basis of subjects studied at school This latter situation may alter in the near future since a number of schools hope to establish something like the British system of " sixth-form " teaching At present the quality of instruction in different schools is so diverse that the university insists on a uniform first year and furthermore regards any attempt to preselect students before entry to this first year as impracticable It follows that the 82 students in the first year feel themselves to be under considerable pressure, for at the end of the year they face a selective examination which must necessarily reduce their number to 60, since this is the maximum the second year can accommodate The first year is thus competitive, and the student tends to regard it as an extension of the school system in which accumulation of examination material is of paramount importance

The first-year subjects are physics, chemistry, and general biology The physics and chemistry are special classes designed for students of medicine, dental science, and agriculture The biology class is not yet in operation, and students are at present taking first-year zoology and a special course in botany for medical students When staff becomes available to give the general biology course, the general and functional aspects of the subject will be emphasised and little purely morphological or taxonomic material will be included The establishment of a combined biology course in place of botany and zoology will leave time for the student to take a fourth subject in his first year, and whether this is desirable or not is still under consideration If a fourth subject is taken, it may well be one which has little immediate connection with medicine It has been suggested, for example, that a special course might be given by the faculty of arts, including the elements of such subjects as logic, philosophy, and English Whatever the precise nature of the first-year course, the main difficulty, so long as there is no preselection, will remain that of inducing the student to alter his opinion that the subjects studied are merely a device for awarding or withholding marks

SECOND YEAR

Much of this attitude persists into the second year, and here too, little can be done about it so long as students are faced by selection at the end of the year It is one thing to know that the normal wastage in the second year may be as much as 20%, and quite another to be told that the wastage *must* reach this figure because accommodation in the third year is limited to 48 places It is probable, therefore, that the attitude of the students will continue (with few exceptions) to be unsatisfactory until they reach their third year at the age of 19

In the second year the student takes a coordinated course in human biology given by the departments of anatomy and physiology The departments function separately, but there is provision for interchange of staff in relation to specific topics, and anatomy teaches some function while physiology teaches some structure Other teachers are occasionally involved, for example, the instruction in hæmatology is supervised by a member of the pathology staff The course covers the main features of the various bodily systems and tissues, and in each the account of the gross and microscopic anatomy precedes the account of function

This course in human biology is coordinated as closely as possible with the instruction in topographical anatomy which begins in the second year In the first term the student dissects the upper limb while the structure and function of the nervous and locomotor systems are being discussed in the biology lectures In the second term he dissects the brain and the thorax during the discussions of the cardiovascular and respiratory systems In the third term the dissection of the abdomen accompanies the study of the digestive, excretory, and endocrine systems It is clearly impossible to organise a complete integration of regional dissection with systematic lectures, but it seems reasonable to try to avoid the usual dissociation which occurs in the student's mind between the lifeless and uninspiring vista he sees in the dissecting room and the functional aspects of his own and other living bodies

Also in the second year is an elementary course in biochemistry It has so far proved difficult to associate this very intimately with the human biology course, because the instruction the biochemistry course contains has to serve the needs of science and agriculture as well as of dental and medical students

At the end of the year the student is passed or failed on the basis of his performance in written examinations, together with a consideration of his practical work throughout the year, as assessed by class examinations, his practical notebooks, and his general performance in practical work The major feature of the written examinations is a paper in which every question demands a knowledge of the relevant anatomy, physiology, and biochemistry Each question in this paper will be marked by two examiners, consulting with the third where necessary

The object is to discourage the student from breaking down the coordinated course into its components again by working for examinations in which the "subjects" are artificially separated. Assessment at this stage has the force of a selection device, and the method adopted is an attempt to ensure that students who are capable of synthesising information are given preference over those who are not. Selection at the end of the second year instead of at the end of the third means that students will be rejected at a time and at an age when they have not yet committed themselves irrevocably to medicine as a career.

In the second year there is a class examination in topographical anatomy, and the "viva" system is in force in the dissecting-room, but promotion to the third year does not depend on topographical skill. Nevertheless, the results of the class and oral examinations count heavily (40%) towards the pass or fail assessment in topographical anatomy, which comes at the end of the second term of the third year.

THIRD YEAR

In the third year most of the process of selection is over—the class is now down to 48 in strength, and further reduction is not necessary, though some normal wastage must inevitably occur. Accordingly it is possible to inculcate a broader attitude of mind in the more receptive students, and to encourage them to think of their studies as a preparation for the practice of medicine rather than a set amount of work to be got through for an examination.

Topographical anatomy continues formally throughout the first two terms, in the first the student dissects the head and neck and is given a course of lectures and demonstrations in general and regional embryology. In the second term he dissects the leg and revises for the professional examination at the end of this term.

Third-year physiology and biochemistry persist throughout all three terms, but in the second term there begins the second of the three coordinated courses in the curriculum. On one day in each week of this term the student visits the hospital. Half the day is spent in studying general pathology, and in the other half he is given, in the atmosphere of the hospital, a talk by a preclinical teacher on some specific biological topic. After this the students will break up into small groups supervised by clinical teachers to see how the applications of the problem discussed work out when observed in hospital patients. For instance, a physiologist might give a talk on the formation of tissue fluid and the possible disturbances of this process, and the student would then be introduced to a patient with œdema. Or an anatomist might discuss the results of section of a peripheral nerve, and the student would then meet a patient with a recovering nerve injury and learn something of his experiences and disabilities.

In the third term of the year three days a week are spent in this way, and instruction in the principles of microbiology and immunity is added. The overlap between pathology and physiology is stressed by both departments, and an attempt is made to show how pathology follows naturally on from anatomy, physiology, and biochemistry. Though formal anatomy has stopped, the importance of anatomy as a sound basis for clinical work is stressed throughout the rest of the curriculum. In the third-term coordinated course, anatomy combines with the departments of child health and psychology to indicate the importance of a knowledge of the processes of physical and mental growth during childhood. At this time also the physiological aspects of menstruation, pregnancy, parturition, and lactation are discussed by the departments of obstetrics and gynæcology. Each student witnesses a normal delivery, and will follow the subsequent history of the child in its home environment as an exercise in social medicine.

During the second and third terms of the third year the student receives the greater part of his instruction in psychology, in the form of a series of lectures and demonstrations. The department of psychology also participates, however, in the fifth-year teaching, in relation to pædiatrics, and again in the social medicine course.

At the end of the third year there will be the professional examination in biochemistry, and also a coordinated examination in physiology and the principles of pathology in which a question on psychology will be asked. Here again the questions will be designed to make the student synthesise rather than fragment his knowledge.

FOURTH YEAR

From the fourth year onwards the students are based on the Royal Perth Hospital, but their connection with the preclinical departments is not wholly severed, for the paraclinical and clinical teachers insist on the importance of an adequate knowledge of the basic sciences. Preclinical teachers may be called upon to participate in seminars or conferences, or to give occasional lectures.

In the fourth year instruction in pathology and microbiology continues. The microbiology class has now a more professional bias, and deals with clinical microbiology and virology; clinico-microbiological conferences are introduced. At the same time pathology becomes systematic, and the student begins to attend necropsies and clinicopathological conferences. These conferences persist weekly throughout his entire clinical education. At the end of the first term the course in microbiology is completed, but the pathology course continues to the end of the second term, during which it contains instruction in clinical biochemistry. At the end of this term occurs the professional examination in pathology and microbiology. In the fourth year also comes the instruction in genetics—a short course of half a dozen lectures relating to the fundamental principles of the subject and illustrated where possible by reference to human disease.

This year also sees the beginning of the student's clinical work proper, and it is now that he does his clerkships in medicine and surgery, six months in each. Three months of each clerkship is spent in the professorial units and the other three months in one of the "firms" directed by other senior clinicians. The formal teaching in medicine and surgery is spread throughout the year, and, so far as practicable, is coordinated with the data presented in the courses in pathology and microbiology. The very nature of the material available unfortunately prevents this coordination from being anything like perfect. The general scheme of clinical work is that in the fourth year, during the period of didactic instruction, students should be as closely associated with the professorial units as possible. In the fifth year they will spread out to study various other disciplines which are either subsidiary or else based on other hospitals, and in the sixth year they return to their main base to consolidate and synthesise their knowledge and experience.

FIFTH YEAR

In the fifth year the student has his formal teaching in obstetrics and gynæcology, pædiatrics, and psychiatry, the lectures and demonstrations in these subjects are spread throughout the year For clinical clerkships the year is split up into three periods of four months, one of these periods is allotted to obstetrics and gynæcology, and one to pædiatrics The clerkship in obstetrics is a resident one occupying two months, and the student will deliver approximately twenty patients In the third four-month period the students study different specialties, such as anæsthetics, orthopædics, otology, and ophthalmology In the course in pædiatrics the emotional problems of growing children will be emphasised with the help of the department of psychology, and in the gynæcology course there will be a series of lecture-demonstrations given by the pathology department

Throughout the year occurs the third coordinated course in the curriculum This course in social medicine takes the form of a series of symposia and discussions, together with practical work organised by the clinical departments in conjunction with the staff of the State Public Health Department, the department of psychology, and others The scope of these classes is wide, and includes such matters as nutrition, vital statistics, delinquency, epidemiology, and the causes and prevention of accidents

At the end of the fifth year there are examinations in the minor specialties These examinations are oral only, and it is represented to the student that the stress laid upon them is of a different order from that attached to the final examinations at the end of the sixth year

SIXTH YEAR

In the sixth year the student returns to his base in the Royal Perth Hospital, and spends the year relatively free from formal classes Instead, he revises and extends his existing knowledge by attending ward rounds, tutorial classes, outpatients, clinicopathological conferences, and other entertainments of his own choosing He also participates in "grand rounds" run on the American pattern by the students under guidance from their clinical teachers

At the end of the year the student faces the qualifying examinations in medicine, surgery, and obstetrics and gynæcology The interpretation of these "subjects" is a catholic one, and there is no hesitation about including questions which demand a knowledge of disciplines other than the one under consideration Thus, a question on the thyroid gland given in the "surgery" paper might expect a demonstration of the candidate's grip on the physiology, biochemistry, and medical treatment of thyroid intoxication, in addition to the pathology and surgical treatment of the condition Similarly, the fact that a given patient is examined by a candidate under the heading of "clinical medicine" does not absolve him from discussing the surgical potentialities of an enlarged group of lymph-nodes There are written, oral, and clinical tests of the candidate's knowledge, and at this stage the presence of external examiners, desirable throughout the course, is regarded as absolutely essential The isolation of Perth makes the problem of supplying and paying for external examiners a very bad one, but it is hoped to obtain examiners from the Australasian area every year, and that they will be regularly supplemented at intervals by examiners from Britain and America

There has been no mention of the subject of pharmacology in the above outline, this is because its place in the curriculum is still uncertain No appointment in pharmacology has yet been made, and it is naturally felt desirable to wait until a pharmacologist arrives before fixing the definitive position and scope of his subject Nevertheless, it is probable that pharmacology will be treated as arising directly from physiology, and indeed the practical work in pharmacology will initially be done in the laboratories of the department of physiology Most of the formal pharmacology will occur in the fourth year, and instruction in the clinical and therapeutic aspects of the subject will be given throughout the later stages of the curriculum whenever the question of treatment arises naturally out of the clinical discussions

Statistics has been given no formal place in the curriculum, but this is not because it is thought unimportant Instead, it has been agreed that each department shall add its quota to the student's knowledge as he passes through it Anatomy, for example, deals with the question of biological variation, the normal distribution, and the meaning of standard deviations Physiology adds to this the methods of comparing means and the assessment of the significance of their differences, in pharmacology the statistical basis of clinical trials and other methods of evaluating the actions of drugs will be discussed, and so on

Discussion

A curriculum such as this is naturally tentative as regards its details As the faculty enlarges, more and more may become possible in the way of individual attention, coordination, and possibly integration At the same time university policy in relation to preselection may alter, making it possible to deal with the students in the early stages rather differently In the future a medical centre may be established, in which case liaison between departments could become closer still It is only by working a system such as the one proposed that its defects and advantages can be assessed, and great care has been taken to avoid any suggestion of finality For the next few years a considerable amount of discussion will naturally take place on the desirability of making alterations, but with every succeeding year these alterations will become less and less easy, and it is intended to lose no time in making any revisions which may prove to be needed

But whatever changes in detail may occur, it is unlikely that the basic principles on which the planning has been founded will alter The importance of looking on teaching and being taught as a cooperative endeavour will continue to overshadow the niceties of curricular organisation, and the education of the faculty by acquaintance with the problems of others will persist as a cornerstone of the future of teaching in Western Australia

This paper necessarily represents a personal view of the curriculum, seen through the eyes of one who participated in its design If one of my colleagues had written it there would no doubt have been changes in emphasis Nevertheless the framing of the curriculum has been in a very real sense a joint enterprise, and what is set out in this article has been agreed to by all It may be that some interest attaches to the names of the new professors in the medical school They are

Anatomy —D C Sinclair, M A Oxon , M D St And

Biochemistry —J W H Lugg, D SC W Aust , PH D Lond , D I C, F R I C , F R A C I

Child health —W B Macdonald, M D Melb , F R A C P

Medicine —E G Saint, B SC , M D Durh , F R A C P

Microbiology —N F Stanley, D SC Adel

Obstetrics and gynæcology —G King, O B E , F R C S , F R C O G , dean of the faculty of medicine

Pathology —R E J ten Seldam, M D Leiden

Physiology —W J Simmonds, B SC., M D Qld , D PHIL Oxon

Surgery —C W D Lewis, B SC , M D , M CH Wales, F R C S

THE BOTTOM OF THE LADDER

HOW TO BE HAPPY THOUGH RESIDENT

W BRYAN JENNETT
M B Lpool, F R C S
LECTURER IN NEUROSURGERY IN THE UNIVERSITY OF MANCHESTER

> " Content may dwell in all stations To be low,
> but above contempt, may be high enough to be happy "
> SIR THOMAS BROWNE (1643) *Religio Medici*

ALL must be residents now Not only those who essay to scale the Moran ladder, or those who choose to extend their clinical education But also those who are anxious, and feel ready, to enter general practice, and those who know they have not a vocation for clinical medicine and are naturally restless to begin one of many valuable careers in the non-clinical field All these must enjoy or endure a year of hospital life They will have a more pleasant and profitable year if they think a little about it in advance

Another Gap in the Curriculum ?

It is accepted that much of the art of medicine can only be taught by precept and example This is too often the excuse for failing to offer any advice at all about matters which are equally difficult to teach by example as didactically Who is to be the example for the dozen or so newly-qualified residents who take up their posts in a hospital on the same day ? Little can be learnt from a visiting consultant about how to survive in a complex closed community twenty-four hours a day for a year Virtually no consultant has been a resident under the National Health Service, and most do not appreciate the extent of the change as it affects the lower orders The neophyte may well be regaled with accounts of bygone days when pay was a pittance and discipline harsh, when the resident had to write letters to the doctors by hand and generally had to do much that today falls to the ancillary staff—and the implication is that the increasing number of ancillaries has eased the life of the hospital resident

It is, however, the very complexity of the staff of the modern hospital that makes the resident's task rather different and perhaps more difficult than previously Departments which previously consisted of one person who could be won as an ally now carry a staff with a hierarchy of its own, competing both within itself and with other departments for prestige and power Radiology, pathology, and physical medicine carry several doctors on their staff, and almoners, secretaries, and records clerks have multiplied and thrown up their own chiefs of department ready to do battle with anyone infringing their unwritten rules " 'That's not a regular rule you invented it just now,' said Alice " All these, in addition to the more familiar triad of patients, nurses, and medical chief, have to be reckoned with by the resident today

Administrator

Administration has been described as an *enabling* process (Taylor 1952) Residents enable the staff of a hospital to work together for the good of the patients, the resident is the only person with all the facts at his disposal —he is the final common path to the patient He is the doctor who sees most of the patient and his relations He sees the ward sister not only on the formal round but also in the evening when the others have gone, when he may hear much about his ward that never comes to the notice of his senior colleagues It is his privilege to accompany his chief all over the hospital and to observe him dealing with patients and colleagues It is he who will talk to the family doctor late at night about a worrying case And so on

If the resident is not prepared to accept the delicate task of liaison officer between all these different persons, and to regard the smooth integration of all their various wishes and demands as his most important task, it will be a pity for everyone and not least for the patients The resident may protest that he came into hospital to enlarge his clinical experience and not to be an administrator He probably thinks of clinical experience as an extension of his final year as a student—seeing and examining as many patients as possible, eliciting signs with greater assurance, and perhaps learning a few techniques If he tries to do just this and neglects his rightful duties, he will learn little of doctoring and may well become one of those sad misfits—the doctor who doesn't get on with people and therefore can never get on with good doctoring If, however, he accepts the challenge of this arduous and skilled task he will learn an immense amount about the management of sick people It is hard to think of a more favourable situation from which to learn this than to be he through whom is mediated everything that happens to the patient in hospital

If the resident has accepted that the task is of this nature, there is some simple advice to offer him—advice which, when written down, seems so obvious that it may seem foolish to state it—but not half so foolish as to forget it

Lines of Communication

Consider personal relations as a problem in communication Almost all personal altercations, whether in hospital or elsewhere, are due to a breakdown in communication Either nothing gets through, or a distorted meaning is put on what does arrive This is called misunderstanding " Oh ! I thought you meant ", " Well, if only you'd said that in the first place ", " I *did* tell you "

So the first rule is to make quite sure that all you say is received in the spirit in which it is meant The surest way to do this is to say it yourself, in person You may then observe the effect of what you say on others, which gives you an opportunity to correct any wrong impressions immediately, to soothe if need be, and even to insist when you read in the recipient's face the quiet intent to disobey If it is possible to write down orders, always do so—an essential where drugs are concerned when this should be made an invariable personal rule Extended to other instructions the written word may save many an argument

Never underestimate the value of the personal approach The trouble taken to appear in person, especially in geographically remote departments, often has a galvanising effect The telephone is the next best Be sure to whom you are speaking and so avoid telling the ward maid to check on the patient's catheter Ask for the sister or the charge nurse, if calling a ward If you cannot speak either directly or on the telephone you are obliged to leave or send a message Defer the whole matter if possible, rather than resort to this unsatisfactory avenue of approach, the distortion a message may suffer is unbelievable If you have to do it, avoid asking a very junior person to bear a message to a senior It is not only discourteous, but the bearer may not have the poise and confidence to convey the message in its full form Do not ask a laboratory technician to ask a consultant pathologist to hurry up and report a biopsy It is always worth the extra time taken to speak directly to the right person

The Other End of the Line

With whom are you concerned to communicate? There are four main groups of people—the patient and his relations, the nursing staff, other doctors, and the ancillary staff of the hospital

The Patient and His Relations

There is no scarcity of written advice about the doctor-patient relationship Most of it applies equally to the patient in hospital as out of it, but there are a few problems peculiar to the hospital situation One is the question of identification of doctors, which scarcely arises when the family doctor's surgery is visited There it is either "the Young 'un or the Old 'un" Not so in hospital, where the only person who, on appearance alone, measures up to the patient's conception of a consultant may prove to be the hospital barber So "state your name and business" and mention your chief, whose name may well be known to the patient and will reassure him If you have to take another doctor to see the patient introduce him properly, by name and trade The same goes for relations, who have a right to know who is giving them what may be momentous news

The informing of the patient and relations about the progress of investigations and treatment is your duty and should not be left to the nurses It is a continual grumble of patients that they are told nothing in hospital The patient must only be told as much as you discern he wants to know Not everyone wants a diagram of his gastrointestinal tract with the ulcer marked in red ink, and this must be respected Those who do not are the patients who say that you are the "doc", or pilot, or captain, and that they leave everything to you This may strike you as an easy and acceptable situation, and so it is if all goes well But, if complications arise and changes in treatment become necessary, they are less likely to take it in their stride than those who have troubled to understand a little and feel they are sharing the responsibility with you for the treatment Well-informed patients are more likely to be able to cooperate in an intelligent way The relations must be told as much as you think they ought to know, and not only as much as they choose to learn or as much as you have the courage to tell We all like to announce good news, and when it is bad we often temper it because we cannot face the full truth ourselves Think imaginatively about the consequences of what you say and you will have a good guide

More will reach the ears of even the least inquisitive patient than you tell him There is the obligatory eavesdropping on student teaching which even the most considerate arrangements can seldom eliminate, the overheard conference between doctors, and even the unwittingly read form with a diagnosis writ large at the top Here it is not so much the truth that you are concerned to conceal as the misinterpretations of stray information out of context that you must correct You will do well after a ward round, whether a teaching one or not, to visit your patients and to sort out what has been said and what decisions reached about each of them Finally, cultivate the bedside manner, not the bed-end manner

Nursing Staff

The ward is the sister's, and I have heard of a hospital where the wards have doors and you ring a bell for admission If you want to go in at a time inconvenient to her, ask, and say why you want to, if you do this from the start you will soon find the ward is yours as well as hers, for as long as you like If you want to carry out any procedure state a time, say what you want, come at that time and, before you start, check that all you want is there

Get clear at the beginning what sister regards as your duty and what hers, in regard to possible areas of dispute, such as filling in forms and ringing up to book appointments in special departments Assume it is your responsibility and, if help is offered, accept it graciously rather than as though you expected it I cannot tell you how unpleasant an atmosphere can be built up in a ward where there is endless disputation about whose job it is to do what

Nurses are in hospital because they want to care for patients There is really no other inducement Remember this, and respect it, and recall from time to time how young the nurses in training are Do nothing to disillusion them about your regard for the patients, for they are remarkably alert to sense when doctors get carried away by their interest in science This may be suspected chiefly of the more senior members of the staff, and it is for you to make up, if need be, for their apparent lack of concern

There are now many investigations which demand the presence of, though often not much actual help from, the nurses Take every opportunity to instruct them, for they will be much the more efficient and cooperative allies for knowing what you are trying to achieve Get to know the seniority of nurses on your ward and their names, and so avoid expecting too much of a nurse just out of preliminary-training school Help them if you can—do not just stand by while they lift beds and patients, give a hand with making the bed you have dishevelled All obvious Yes, but these things never occur to most young doctors in hospital

Doctors as Colleagues

There are three groups of doctors those on your own firm, others in your hospital, and those outside The bigger the staff on the firm the more difficult is your task You will have to keep them informed of each other's decisions and plans from day to day Do what you are told when you are told, not when you think you will Make it a rule to see that the chiefs know all major events—some will want to know a lot, and some a little, but always err on the side of telling them too much Remember a patient's relations or his family doctor may ring your chief up for information, or he may meet them socially Imagine his consternation when asked why one of his patients has died and this is news to him

So far as other hospital doctors are concerned, try if possible to make contacts on your own level The circumnavigation of what in Army parlance are called "normal channels" is a common reason for offence being taken Most such "crimes" are quite unintentional, as when a resident rang a hospital to transfer back to it a patient who had completed surgical treatment He asked for the appropriate ward, and to his surprise the consultant answered the phone That resident's Board of Governors had a letter next day complaining of the matter and requesting that in future the house-physician and not the consultant should be rung up If unusual methods of approach are being used, and it is right and proper that they should be on occasion, show that you know that they are before you are reminded abruptly The phrase "I am taking the liberty of" pays dividends in good will

When you have dealings with a doctor outside the hospital remember that it is your chief and not you that he knows and whom he really wants to deal with Don't haggle on the telephone, just say you will have to ask your chief, if the line of action is not an obvious one Each firm has its own way of dealing with requests for urgent admissions, and you must tell the doctor about this—namely, that your instructions are, &c You must on this, as on many other occasions, gently remind your listener that you act for another, and, although you may not like too much the sound of "I am only doing what I am told", it is the soft answer which turneth away wrath Provided it is true.

If you have to write a discharge letter, think what the doctor wants to know Don't burden him with a long history which he will already know if he really cares and, if he does not, will not be interested to learn Tell him what your chief thought about the diagnosis, if need be, say that no conclusion could be reached And tell him what to do, what drugs you recommend, and say, if possible, how long off work you recommend Yet keep it all short, for the busy doctor has not time to read an essay on pernicious anæmia, when what he wants is the diagnosis and the dose of vitamin B_{12} you advise If he wants the essay, it will be elsewhere in his post, and the back of it can be used for blotting Tell him if the patient dies, because he is even more open to the hazards of being confronted by the family

Doctors as Patients

There is another doctor you may meet occasionally, and that is the doctor who is a patient or a patient's relation Do not expect him to treat you with quite the respect you will have come to regard as usual from the laity, if you are doing your job well He will be ever striving for words with your chief, and reasonably so You will do your best to see that he has reasonable access to him None the less you can, while according him some privilege in the Hippocratic tradition, see that the situation is kept under control, and that he is not allowed to badger the nurses and yourself to the detriment of good order and discipline and the welfare of other patients If he doubts the advisability of any investigation or treatment, say that it is the express wish of your chief Again you must assume your ambassadorial role, and on occasion take on the authority of him whom you represent There will be few doctors who do not realise that, having worked with your chief for some time, you are likely to know best what he would wish It should be obvious that, if a doctor's relation presents for urgent treatment—e g, through an accident—you should immediately call in someone more senior The thought of cheap glory is as nothing compared with the odium you will incur if your perfectly reasonable treatment goes astray through no fault of your own It is a responsibility with which you should not burden yourself Never forget the simple fact that, if the chief's wound breaks down, it is due to bad germs, but if yours does it is due to bad surgery You cannot build up in six months what has taken your chief twenty years, and he needs every bit of his reputation to weather the vicissitudes of treating a fellow doctor or his dependents

Ancillary Departments

Most of what has been said applies to dealing with these departments, with especial emphasis on the fact that you are carrying out your chief's wishes Residents sometimes have to take the most awful dressings-down from quite junior members of these departments as a consequence of doing exactly what they have been told It is quite wrong that these doctors should be bullied in this way, but I suspect that they may sometimes have created a difficult situation for themselves by a tactless approach Demands for urgent examinations are perhaps the commonest cause of trouble Providing there has been no delay on your part in making a request of this kind, counter any resistance you may meet by offering to ring your chief and ask him if he is prepared to forego this investigation This facilitates matters greatly, and rarely costs the hospital a telephone call If, of course, you have had a request in your pocket for a week and suddenly realise your chief will be starting his round in an hour, you will have to go cap in hand to the appropriate department. Whether you get roundly ticked off both there and later by your chief will depend on how well you have fostered relations up to date It is amazing what departments will do for those who are *persona grata*, and how obdurate they can be to those who are not

The fact that so many hospital departments close at 5 P M. is the target for much ill-earned abuse Remember that a great deal of laborious routine work goes on to provide you with results, and without the excitement and rewards of clinical medicine It is presumptuous to expect them to work regardless of time or effort in the manner commonly taken for granted in clinical doctors, however ill-deserved we may sometimes feel this assumption to be So comply with rules for sending in requests early in the day, and if you have to ask someone to stay on late or come back into hospital see that they realise just why you have called them in, and let them see how reliant you are on their services If necessary do not be afraid to dramatise the situation a little, especially if dealing with lay staff It is remarkable, for example, the effort and imagination office staff will expend in a search for notes or the like if they are allowed to see how vital it is

Conclusion

There will be some who think that I have painted, by implication, far too grim a picture of hospital life Some, perhaps, will put this paper down thanking God they are not as other men are, and that *their* hospitals are happy ships, anyway I have had the good fortune to work in several teaching hospitals in different parts of the country, and in regional and Army hospitals too I am most impressed with how similar the pattern of hospital life is under varying conditions, and that a hospital is no better than the doctors working in it However grand the names on the board in the vestibule, it is the residents who give the hospital its real reputation—its reputation in the community which it serves

A current British tome devotes space to discussing whether the family doctor or the visiting consultant should precede the other into the sick-room in the patient's home This concerns few patients and fewer doctors The number of doctors and patients who have to work out their salvation in hospital is large, and increasing I believe we must get over our shyness of talking about how we should deal with each other and with the many others whose paths cross ours in hospital

REFERENCE

Taylor, S (1952) *Lancet*, ii 31

ACADEMIC REVOKE AND FAILURE AMONG OXFORD UNDERGRADUATES *

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THE diversity of grants since the war has much increased the pressure on students to work hard at Oxford University Academic demands have therefore imposed stress from which the unstable may all too easily run away This paper deals with this running away from work or examinations it prescinds from the question of simple work panic, already fascinatingly covered by Malleson (1957)

Material

100 Oxford undergraduates were closely studied while under psychiatric care at the Warneford and Park hospitals, Oxford, between 1951–4 Their mode of selection has already been described (Davidson et al 1955, Spencer 1957, p 93)

These 100 student patients were found to divide diagnostically into 12 psychotics (P group) and 88 neurotics, the neurotics subdividing into 48 hysterics or behaviourally disturbed (H subgroup), 10 depressed schizothymes (D subgroup), and 30 simple affectives (A subgroup) these divisions are described and discussed elsewhere (Spencer 1957, pp 98–105 and 207–18)

Definition

Academic revoke can be gross or partial and can be from ordinary work or examinations, as table I shows The forms are fully defined in my thesis (Spencer 1957, p 163 and pp 165–6) In summary, gross work or examination revoke means running away from essay writing or other study, examination revision, or the examination itself the run away is usually physical but occasionally (in 2 patients of the group) is mental and entails the patient sitting over the essay or examination paper, day-dreaming The revoker, says Farnsworth (1956) " has dozens of intricate ways of postponing or avoiding work He plays solitaire, goes to the movies, sharpens pencils, puts his room in order, visits all his friends down the hall, plays some records, and still, when he starts to study, his mind won't do its bidding and focus its attention on the subject assigned " The situation evokes a parody of the saw, " I eats well, I sleeps well, but when I sees academic work, I comes over that bad "

Partial work or examination revoke, though still found largely among hysterics, corresponded more to Malleson's (1957) work panic, of poor academic concentration with a marked tendency to distraction, the condition becoming exacerbated by worry into a vicious spiral which may culminate in running away

Results

INCIDENCE

As Trigger

Among 133 *factors triggering the illnesses of these* patients (or 1 33 per patient), academic trouble appeared in 42 cases, coming second in importance only to trouble with personal and sexual relations (which triggered 44 illnesses) 22 of these 42 cases pushed over the brink by work problems were in H subgroup

As Symptom

Besides these 42 cases triggered by work problems, 4 others had academic revoke as a symptom, making 46 cases in all Table I shows the incidence of academic revoke In 14 cases, all in H subgroup, it was the major factor producing breakdown

The distribution among the subgroups of patients is displayed in table II The predominance of the hysterical subgroup is clear Indeed, it is worth regarding each case of gross academic revoke as in this subgroup unless other evidence points to psychosis (as in 1 cyclothymic case in the group), or depressed schizothymia (which in many respects is close to hysteria) (Spencer 1957, pp 210–11) Note how well the As kept at their studies and examinations

PHYSIQUE

Gross academic revoke correlated significantly with endo/mesomorphy (or ectopenia), a mixture of fat and muscle (ectopenia 3^2 or less, r=0 41*) †

Partial revoke correlated with mesomorphy or muscularity (4+, r=0 42*)

The 14 cases, whose revoke was the major factor in their breakdown, also had significantly endo/mesomorphic physiques (ectopenia 3^2—, r=0 46*)

Figs 1 and 2 display the somatotype distributions of the gross revokers and those in whom it was the main catastrophe It will be seen at a glance how work revokers congregate to the left of the somatotype chart, where the extroverted hysterics predominate (Spencer 1957, p 134)

TABLE I—INCIDENCE AND FORMS OF ACADEMIC REVOKE

—	Work revoke	Examination revoke	Total
Gross	13	9	22
Partial	22	2	24
Total	35	11	46

TABLE II—ACADEMIC REVOKE AND SUB-GROUPS OF PATIENTS

—	P	H	D	A	Total patients	Correlations (totals only)
Gross revoke						
Total	1 (8%)	19 (40%)	1 (10%)	1 (3%)	22	H—r—0 70**
Work	1	10	1	1	13	
Exam	—	9	—	—	9	
Partial revoke						
Total	3 (25%)	13 (27%)	3 (30%)	5 (16 5%)	24	
Work	3	13	3	3	22	
Exam	—	—	—	2	2	
Total academic revoke	4 (33%)	32 (67%)	4 (40%)	6 (18 5%)	Gr d total 46	Gross & partial H—r= 0 59** A—r= —0 56**

P=psychotics, H=hysterics, D- depressed schizothymes, A=simple affectives

TABLE III—ACADEMIC REVOKE AND FINAL RESULTS

—	Gross academic revoke	Partial academic revoke	All patients	Correlations
1st	1 (5%)	—	6 (6 5%)	
2nd	3 (15%)	11 (48%)	39 (44%)	Gross v rest eligible r=0 52**
3rd	4 (20%)	5 (22%)	23 (25%)	
4th, pass, sick, failed or down without sitting	12 (60%)	7 (30%)	23 (25%)	Gross v rest eligible r=0 62**
Total eligible	20	23	91	
Postgraduate or still to complete	2	1	9	
Failed or down without sitting	7 (35%)	4 (17%)	15(16 5%)	Gross v rest eligible r=0 45*

* = significant at 5% level } on χ^2 test using Yates modification
** = significant at 1% level } where necessary

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* Based on part of a thesis submitted in 1957 for the Doctorate of Medicine of Oxford University

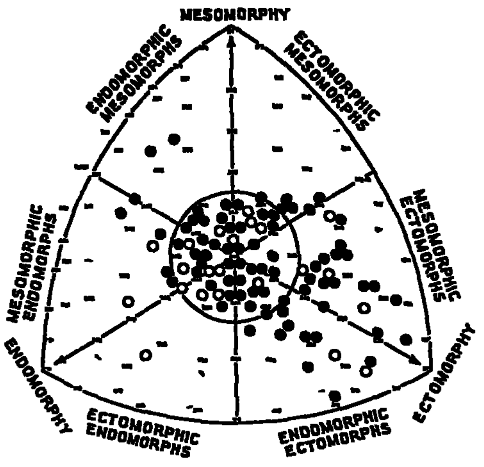

Fig 1—Somatotype distribution of 100 undergraduate psychiatric patients
○=22 cases of severe academic revoke,
●=rest of patients

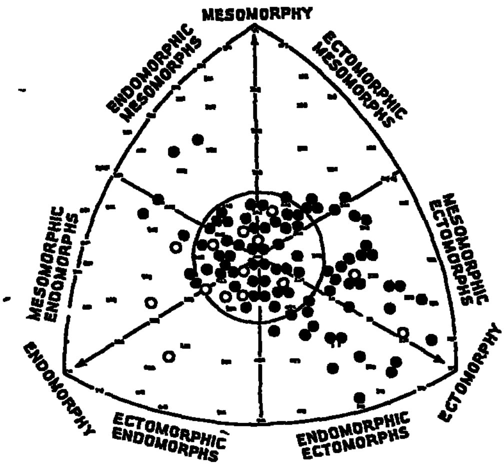

Fig 2—Somatotype distribution of 100 undergraduate psychiatric patients
○=14 cases ill mainly through academic revoke,
●=rest of patients

EXTROVERSION/INTROVERSION

Both gross and total academic revoke correlated very significantly with extroversion, with which, estimated on a 7-point scale and at the level of 3 or more, the respective rs were 0 54** and 0 60**

MINNESOTA MULTIPHASIC PERSONALITY INVENTORY

Taking 70 or more on any subcategory as criterion of instability and compared with the rest of the patients, the gross revokers had a small positive correlation (r=0 12) That of total revoke was higher (r=0 28) but not significant

INTELLIGENCE AND ACADEMIC RESULTS

On AH5‡ total scale, no significant difference among the revokers could be found either from the remaining patients or from a group of 100 controls similarly tested

Yet, as table III shows, the academic results of these revokers were far worse than for the patients at large—who, psychotics and these failures apart, were comparable academically with normal undergraduates It is interesting that the figure of 60% of gross revokers getting low or no academic degrees is identical with that for the psychotic patients

Management

Partial Revoke

The partial revokers largely responded to simple psychotherapy Our usual method was to explain to the patient that the more he fought the distraction, the worse it would become His preferable recourse was to break off work and give full play to the distraction for a period fixed by the clock, 5–10 minutes At the end of that time, unless he had by then found a solution to the distracting problem, he should say, as if to an intruding child, " Well, that's all I've time for now, I'm afraid, I'll think more about you later ", and return to his study This technique might need several repetitions

Gross Exam Revoke

The management of severe examination revoke when seen in time was forceful persuasion back to the examination However, in the case of the most severe instance of it, in which the patient had an hysterical fit while sitting in the front desk of the front room in the first minute of the first examination of Finals, he had to be transported with paper and invigilator to the Warneford Hospital, where he was eventually persuaded to sit the offending and subsequent papers he obtained first-class honours

3 of these cases revoked successfully, one before he was under care

Gross Work Revoke

This type of revoke affected 13 patients 4 made successful getaways 1 was concurrently drinking and, the alcoholism treated, the revoke ceased 2 scraped by on their own

For the remaining 6 a technique was worked out by Miss M A Davidson and myself which, although laborious, paid a dividend in reasonable degrees for all but one, who went down without The patient was brought daily to hospital, taught (by Miss Davidson) the basis of methodical study of which all were previously ignorant, and then sat over by therapist or delegate during the period of study in a room barely furnished and without distractions Prestige, enjoyment of being mothered or both kept the patients at the grindstone, and none of them walked out of this voluntary, solitary confinement before their allotted break

Discussion

General immaturity of personality is a notorious feature of the extroverted, Eysenckian hysteric running away from responsibilities is characteristic of the immature In academic revoke, then, we have a tangible, frequent, and largely objective measure of immaturity in undergraduates

The severe degree of it is markedly disabling in terms of intellectual wreckage and the inordinate time dons have to spend in salvage attempts, particularly when it is borne in mind that the intellects on the rocks of this condition are of average Oxford University potential and therefore above the 95th general population percentile

For one case deep analytical therapy was recommended by a London psychiatrist, failing to recognise that this is academically an intensely distracting undertaking even for the well poised for the academic revoker it provides a certain excuse

" Continuous pressure " therapy as here described is the only type known to achieve sporadic success As it is

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† All correlations are tetrachoric
* = significant at 5% level } on χ^2 test using Yates' modification where necessary
** = significant at 1% level
‡ A test designed to differentiate undergraduates

time-, staff,- and morale-consuming, it can be applied only by a coherent and adequately staffed psychiatric service for students

This condition—wherever it exists—constitutes, therefore, an important argument for an adequate psychiatric unit for the treatment of undergraduates and, perhaps, for a formal university service

Summary

Academic revoke—from work or examinations—triggered or helped trigger the illnesses of 42 of 100 Oxford undergraduate patients

In 4 others, making 46 in all, it was a prominent feature of the illness In 14 it was the major feature of the breakdown Gross revoke occurred in 22 cases, partial in the remaining 24

The revokers were predominantly in the hysterical neurotic subgroup, fat and muscular in physique, extroverted in personality and more than averagely unstable, even for a patient Though normal in intelligence, their academic results were poor compared with those of psychiatric patients at Oxford in general

Special techniques had to be devised for their management, particularly " continuous pressure " therapy These techniques require large therapeutic staffs and therefore argue for an adequate university psychiatric service

The research underlying this paper was carried out on subjects under the clinical care of Dr R G McInnes and Dr J S I Skottowe Dr R W Parnell supervised the research and performed the estimations of physique Miss M A Davidson, whose therapeutic work has already been mentioned, tested psychologically all these patients

REFERENCES

Davidson, M A, Lee, D, Parnell, R W, Spencer, S J G (1955) *J ment Sci* 101, 810

Farnsworth, D L (1956) Mental Health in Colleges and Universities, lecture iv, Lowell Institute Lectures

Malleson, N (1957) *Brit med J* ii, 551

Spencer, S J G (1957) Comparative Study of Psychological Illness among Oxford Undergraduates D M thesis, University of Oxford

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WHAT SHOULD THE STUDENT LEARN IN GENERAL PRACTICE ?

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MEDICINE in hospital is essentially different from medicine in general practice Not only does the hospital case-load differ in age and stage of disease but the function of the hospital is primarily curative or restorative, whereas often the main tasks of the practitioner are to keep watch or help the patient to delay his handicaps and adjust himself to them

Recognising such differences, most medical schools are now concerned to teach general practice, or at least to show the final-year student what morbidity outside the hospital looks like But to farm students out to general practitioners for short periods is hardly enough What has to be taught is the application of the principles of medicine in the setting of general practice

The special characteristic of the general practitioner is that his interest in medicine is limited neither by site nor age His role, properly played, gives him a unique relationship with his patients, and he is " liar, physician, hypocrite, and friend " He is also, potentially at least, much more He is, or should be, the integrator of the Health Service To the patient, through most of life, the hospital, consultant, and local-authority services are largely peripheral they exist to support the general practitioner to provide comprehensive medical care The practitioners should be able not only to draw on these and many other services, as he interprets his patients' needs, but also to practise prevention—not *primary* prevention (such as is associated with sanitary engineering or immunisation) but *secondary* prevention by anticipating and trying to delay the degenerative diseases With improving techniques for the control of disease, early diagnosis has become of more than academic interest, and the general practitioner has more chance than anyone else to discover and bring forward cases at a stage when specialised knowledge can be applied effectively To do this he needs clinical skills much the same as those of the specialist, but he will apply them in a different way, seeking a presumptive rather than a definitive diagnosis

Because it involves seeing so many people with varying needs, general practice involves another technique—the organisation of resources and particularly of time The practitioner should regard his surgery sessions as essentially a filter, allowing him to separate off those cases he wishes to investigate or treat more thoroughly At crucial stages of both physical and emotional illness, it is very often worth investing 30 minutes—if only because this will reduce the number of attendances

If this is general practice at its best, how can it be taught? Even for students with prior indoctrination (which few curricula provide), observation *is* not enough, for there are few practices where the new possibilities of general practice have been realised to the full To break the new ground experimental models are needed Just as the teaching hospitals finance research and set the standard for conventional specialties, so the medical school must conduct research into, and set standards for, general practice

Faced with this problem, Manchester University made a contribution by setting up Darbishire House as an experimental health centre This brought under one roof four local general practitioners whose combined National Health Service list amounted to 11,000 The physical amenities essential to good general practice were provided, together with X rays and facilities for pathology District nurses, a social worker and health visitors, and clerical help have also been enlisted Rooms were provided for maternity, child-welfare, and school clinics, all run by the practitioners and the health visitors, thus integrating the local-authority services and general practice

Although observation in itself is not enough, it is none the less important in showing students what general practice means They come to the centre in groups of four for two weeks and are attached individually to the doctors Each morning is spent in the surgery, where some 300 patients will be seen in the fortnight, and visits made to 100 homes This allows intimate observation of the patients and their families, and in turn each practitioner selects a sick family for the student to study and present to the group Even in this short time a close relationship may develop between the student and his tutor " truly ", as one of the doctors has put it, " more than the calf yearns to suck, the cow loves to suckle " (Davie 1956) Indeed, one of the risks of apprenticeship, in general practice as elsewhere, is that the apprentice's respect and affection will weaken his critical faculties and cause him to absorb bad habits and ideas as readily as good ones

The afternoons are given to group discussion In our experience, the student has little grasp of the philosophy of comprehensive medical care or of the relation of medicine to the State On the first day, therefore, there is full review of the historical and cultural evolution of the N H S and its economics This helps to orient the student and to foster an awareness of the potentialities of the present structure, and of the resistances to further progress

Thrust from the hospital, with its goal of definitive diagnosis, into general practice, where diagnosis is usually at most presumptive, the student is frankly lost He has to recognise that the goals are different and that the general practitioner applies the principles of medicine in a particular way Because the investigation in general practice is usually made at an early stage (largely unknown to the hospital), the doctor is concerned with possible developments or regression rather than specific pathology

It is in this light that the student should consider the use of some clinical skills which have too often lapsed, or never fully developed, in British general practice—e g, hæmoglobin estimation, erythrocyte-sedimentation rate, test for occult blood, and the use of the microscope He should also consider the use of old tools not for individual diagnosis but for screening, in attempts at presymptomatic detection of common and chronic diseases of middle and later life—e g, weighing, blood-pressure, enzyme tests of urine for albumin or sugar Then there are tools which the practitioner could use not so much to define abnormality precisely as to satisfy himself either that the situation is under control or that specialist consultation is required—the ophthalmoscope, swabs for culture, wet X-ray film, cervical smears (Papanicolaou), respiratory flow-meter, simple electrocardiography He will not seek to diagnose sarcoidosis or localise the infarct, rather will he use these tools to prompt earlier specialist help

Much ambulant or housebound morbidity arises from the common chronic degenerative diseases affecting lung, joint, heart or mind Unlike the kinds of disease treated in hospital, these require long-term care by the practitioner, and adjustment to lifelong handicap Here the doctor has to cooperate with other agencies in aftercare—the health visitor or the disablement resettlement officer for the sick worker before he becomes too old or chronic to retrain or rehabilitate These social skills are used in the same way in delaying incapacity among the elderly in the home To complete the picture, students visit an industrial rehabilitation unit and a geriatric unit Since a third of general practice has predominantly emotional aspects, new ways are tried, such as first-aid by counsel to the family In such cases the student can be shown how much more benefit people may get from half an hour's simple psychotherapy—at some critical time such as childbirth or retirement, perhaps—than from repeated short, and unsatisfying encounters

To absorb such a programme in a fortnight is too much for many students, and the time could with advantage be doubled The real need is for the student, during his hospital years, to bear in mind that throughout his life the patient has medical, social, and emotional needs beyond those calling for episodic concern from the hospital

The Darbishire House programme is only a beginning Perhaps the most important lesson from it so far is the realisation of how far we have still to go

REFERENCE

Davis H M (1956) *Manchr Univ med Sch Gaz* 35, 3

MEDICAL STUDENTS AND GENERAL PRACTICE *

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DURING three years' clinical work as medical students at the Royal Free Hospital we become acquainted with many specialties, but of one branch of medicine we catch only a glimpse, and that is general practice The system of "sitting in" with a general practitioner helps to give a better view and to clarify and readjust our ideas about general practice

As a final-year student I attended, once a week for three months, the evening surgery of a general practitioner in Hampstead in N W London This was a worthwhile and enjoyable experience, and I am going to comment on the ways in which these visits helped me

A continuous fortnight in general practice, attending all surgeries and domiciliary visits, might give a better overall picture of a practitioner's life, but attendance once a week for three months has the advantage that patients' progress can be followed over a longer period of time

The Benefits

There were four main benefits I gained from these visits

Firstly, I saw the actual running of a general practice and how conditions differed from those in hospital I could examine the system of keeping patients' case-records and the things the doctor had in the surgery to aid clinical examination. I also saw to what extent he could command laboratory and radiological investigations I could discuss with the doctor the effect of the National Health Service on his practice and see the clerical aspects (registering patients, certification, and so on) as they arose I saw how much time could be devoted to patients with illnesses of varying severity in a crowded and ever-enlarging surgery

Secondly, it was interesting to see patients in their own environment on domiciliary visits In hospital a patient seems detached from his own environment, and it is hard to picture the repercussions of his illness on his own and his family's life

The environment often influenced the patient's treatment for example, could this old lady living alone walk down two flights of stairs to get to the chemist's shop for a prescription? Small practical points played a very large part in deciding treatment Could a patient stay in bed for any length of time when he could not afford to stay away from work? Who will look after the patient confined to bed? Can relatives or a nurse be found to care for the children or clean the house of the sick mother? These problems are not always obvious to the student in hospital

Thirdly, I was able to see the general practitioner's difficulty in assessing the significance of mild and early symptoms in a patient seen for the first time There followed the problem of whether these symptoms merited a specialist's treatment, home treatment, or any active treatment at all I was often humbled to discover that what seemed to me to be a complicated and serious diagnosis was considered by the practitioner to be a more common and straightforward condition, requiring only simple but practical treatment It became clear that common complaints do commonly occur

Lastly, it was obvious how many patients at any one surgery have symptoms partially or wholly due to anxiety states I was fortunate in "sitting in" with a doctor particularly interested in psychological medicine I was able to see how his questioning revealed the psychological nature of the patients' complaints and how much they benefited from sympathetic listening, understanding and discussion of their problems

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* Based on a paper read at a meeting of the North London Faculty of the College of General Practitioners on April 29, 1958

A Popular System

This method of taking a look at general practice has gained in popularity among the students at the Royal Free, so that 40 out of approximately 60 eligible students sat in with a general practitioner during 1957–58, and 33 have already applied during the first six months of 1958–59 This system began in 1953, when students in the last eighteen months of their clinical work could sit in with a general practitioner for two weeks if they wished Later, in 1957, the system of attending once a week for three months was introduced and proved to be more convenient for many of the doctors and students

During 1957–58 two students lived in for one week with a general practitioner in a Derbyshire mining community, and they were able to see all the difficulties in this particular type of practice

The total of 40 out of 60 students in 1957–58 shows the growing interest of students in general practice 10 students who had lately visited practitioners were asked for their views They were unanimous that their sitting-in had filled a gap in their knowledge and had clarified their ideas about the practice of medicine outside hospital 6 of the 10 felt more attracted to general practice and 3 of the 6 felt fairly convinced about entering general practice 4 of the 10 thought that psychosomatic medicine played a significant part in general practice 4 more agreed with this viewpoint on direct questioning All agreed that this scheme is worthwhile and useful, and we are all very grateful for the help we have received from all concerned

I should like to thank Dr Philip Hopkins for his help and interest, which have enabled this article to be written

LEARNING MEDICINE BY CLINICAL PRACTICE

HOME-CARE PROGRAMME OF BOSTON UNIVERSITY

Gerald Hass

Clinical Student

THE LONDON HOSPITAL MEDICAL COLLEGE, LONDON, E 1

Since 1875 final-year students of Boston University Medical School, attending the Boston City and Massachusetts Memorial Hospitals, have taken part in a Home Medical Service For one month, a small group of students act as general practitioners providing domiciliary medical care for the indigent and otherwise doctorless population near these hospitals

The aims are not only to ensure that the patients receive adequate medical care, but also to introduce students to the practice of medicine in the home, to make them aware of the problems of public health, to give them an appreciation of the patient in his environment, and to relate this to the principles and practice of preventive medicine

I here describe the scheme as seen through the eyes of a fourth-year English medical student who spent a month last summer working with, and under the same conditions as, a group of four American students

The Scheme

The headquarters in the outpatient department of Massachusetts Memorial Hospital consists of a large conference room, equipped as a laboratory for simple investigations in hæmatology and bacteriology A refrigerator contains stocks of penicillin and blood-agar plates, and round the walls are cupboards filled with many free samples of pharmaceutical products

Each student is assigned an area near the hospital, which represents his practice Some areas are large, and all contain between 1000 and 2000 prospective patients Often a car is necessary, since visits may involve much travelling

The student's equipment consists of diagnostic instruments, thermometers, throat-swabs, and a few drugs (aspirin, phenobarbitone, ephedrine, adrenaline, and penicillin) He also carries 'Clinitest' tablets for urine analysis, the equipment necessary for Mantoux tests, and a supply of prescription forms countersigned by a member of the medical staff All this is in the traditional black bag which serves as a badge of office and ensures a safe journey in the less savoury parts of town Lollipops are useful bribes for young patients and are kept in the conference room's store of drugs The student may prescribe any drug he thinks fit—except narcotics Prescriptions are dispensed at local drug stores or at the hospital pharmacy

Students work six days a week, beginning at 8 A M and usually finishing by mid-afternoon A supervisor, who is a full-time member of the department of preventive medicine, is available for consultation at all times and will advise students by telephone

At 8 A M a conference is held and the previous day's cases are discussed Patients' telephone calls are received by a nurse who notes the complaint and allocates the case to a student. No cases except emergencies are accepted after 10 A M , and after the conference the student sees his new cases and revisits old ones It is rare for one student to make more than a dozen visits in one day

Each student also has a list of about 6 chronic patients, usually old people, to be visited once or twice a week District nurses provide bedside care for these patients, and the student is expected to supervise management, prescribe drugs, and (most important) to maintain the patients' morale

If the student thinks fit he may refer patients to outpatient departments or arrange their admission He is expected to follow up his cases and accompany them to their specialist consultations

The full notes kept by the student record the history, examination, diagnosis, treatment, and course of each case These can be referred to in future illness and are valuable for statistical analysis

The Patients

Those who earn less than $40 monthly (for a single person) are eligible All those receiving relief or other financial aid from Federal and Civic resources are automatically eligible For each medical visit $2 20 is paid to the home medical service by the relief oraganisations Every year domiciliary medical care is provided for approximately 5000 patients

I made 130 visits to 40 patients, half were children under ten years, and most of the others were over sixty These figures tally with the averages obtained by the department over the course of one year It is interesting that of all the patients treated in hospital for that year only 20% were children under ten and 10% were over sixty The reason for this disparity may be that many children and elderly patients are not ill enough to need admission or that the home-care scheme encourages them to seek advice more often and for less reason

By far the largest group of patients I saw were children with upper respiratory infections, tonsillitis, and otitis media Other conditions included measles, mild gastroenteritis, and a congenital heart defect Older patients were mainly chronic invalids needing supervision and management (heart-failure, rheumatoid arthritis, and the multiple complaints of old age not bad enough to need admission) Among the adults I saw seborrhœic dermatitis, angioneurotic œdema, a family with suspected pulmonary tuberculosis, a patient in a severe agitated depression, and a sprinkling of functional disorders of no known cause

I used a portable hæmoglobinometer, made blood slides, and did differential white counts I cultured throat swabs on blood-agar plates and became fairly proficient in these minor investigations after a short while

In all, about a quarter of the cases I saw were referred to hospital outpatient departments by my letters. These included requests to skin, E.N.T., and X-ray departments. Most of my patients had upper respiratory infections, so prescribing was straightforward. All treatments were discussed with the supervisor, and, in difficulty, helpful advice was always forthcoming.

Many patients had social problems which were beyond my scope, and the social worker attached to the scheme was a great help in investigating conditions in the home and providing financial and other aid, which was particularly needed for old-age pensioners.

The Benefits

The attitude of American students to this month's work is one of keen interest, coloured by a certain amount of trepidation. Here at last is an opportunity to put into practice part of the theoretical knowledge acquired in medical school. They regard the month as an easy one in terms of man-hours, since there are no formal lectures and tuition. Instead, conferences and discussion make them feel that they are responsible doctors interested in the welfare of their patients. They learn the importance of conscientious clinical work and integrity in social dealings with their patients and as a part of this gain insight into the living conditions of patients.

The medical staff feel that the scheme does much to mature the student's approach to his profession. The lack of confidence he feels in his own ability is soon dispelled when he realises that advice and help are always available. The important thing is that *the student* stands on his own feet, is the first person to see the patient, and it is on him initially that the onus of diagnosis and treatment rests. It is he who brings into action the various social services. This is very different from the Edinburgh scheme (Scott 1950) where students are introduced to patients by a general practitioner. Only after a few visits with the practitioner is the student allowed to follow up a case—which has already been assessed, diagnosed, and treated for him.

My own opinions of the scheme are very similar to those of the American students. They may have been affected by the fact that I had only a short while to adapt myself to a new environment and different ways of working, and I was an object of friendly curiosity to my colleagues and patients. The scheme was a particularly stimulating experience because I was able to see, in detail, a side of life in Boston seldom seen by tourists. I felt, as did my colleagues, that I was doing something worth while, though just how much I gained is hard to assess at present.

Among various criticisms, the most obvious is that students are not yet fitted for the responsibility of treating patients in their homes. The scheme is said, therefore, to be detrimental to the interests of patient and student. It is my impression, however, that the advantages outweigh the theoretical possibilities of the student failing to cope successfully. Perhaps the best indication of this is the fact that for over eight years medical students in Boston have been doing valuable and conscientious work in caring for their patients.

A project like this might be an advantageous part of medical education in this country, even though the National Health Service provides adequately for the indigent.

I am very grateful for the help received from the governors of The London Hospital Medical College. I am also grateful to Prof. H. Bakst, of Boston, for his hospitality and to Dr. J. R. Ellis for having made this visit possible.

REFERENCE

Scott, R. (1950) *Lancet*, ii, 695.

DISCUSSION GROUPS FOR PÆDIATRIC STUDENTS

VICTORIA SMALLPEICE
M.A. Oxon., M.D. Lond., F.R.C.P., D.C.H.
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FOR the past ten years medical students on the pædiatric firm at Oxford have been asked to read papers on some specially selected subject. The general plan has been modified from time to time and it is useful at this stage to look back and try to judge what type of question has interested them and produced the best work.

Students on each obstetric firm are attached to the pædiatricians for three months and during this time they learn something of the care of the normal and sick neonate and the premature baby. Shortly afterwards they spend three months in the general pædiatric department, the firm usually consisting of five to eight students with a maximum of ten.

Object of Papers and Discussions

The object is to give every student an opportunity to investigate some problem during the last month of his pædiatric course. A subject is chosen which is suitable for presentation by the group. Each student is limited to twenty minutes for his paper and members are asked to study the historical background and literature and, when appropriate, to illustrate their work by graphs, X-rays, and photographs; case-histories and data are taken from the Children's Department. Where the choice is a happy one, it gives scope for the very different interests and approach of the individual students and they are left to divide the work to suit themselves.

In preparing their papers they learn where to find the information they need, how to get help from all those interested in the child, and the ways in which we attempt to coordinate the various services. They get experience in setting out their work, keeping to a time limit, and arranging the papers among themselves so that these are complementary rather than redundant. A number of sessions have been of real value to me personally in throwing a new and critical light on our problems, and it has been particularly interesting to compare surveys made at intervals of some years on a similar subject.

General Plan

Two sessions are now usually held for each firm. One of these takes the form of a supper at my house followed by papers and a general discussion; a guest may join us for the evening and pathologists, registrars, or housemen may come in time for the papers, but the party remains a small one. The second session usually replaces an afternoon ward round and is used for a more general discussion with perhaps a general practitioner, medical officer of health, and social worker as guests. At these, too, the numbers are limited and less than twenty people take part. All the students come to both sessions although they read papers at only one.

Some Subjects Chosen

Afternoon Sessions

(i) Study of a Hutted Camp. An abnormally high proportion of children admitted to the wards came from a hutted camp some miles from Oxford and one firm was asked to consider this. One student opened the discussion with a general review of the literature on child health and environment. Another had visited the site and taken excellent photographs to illustrate his paper, the general practitioner had helped him in his investigation and joined us in the discussion, bringing his social worker with him Two students had studied the case-histories of children admitted from the camp, particularly with reference to any possible influence of their environment on their illness, their need for admission and their subsequent progress The medical officer of health helped the students to collect their data and joined us at the session

(ii) Discussion on the problem of Repeated Respiratory Tract Infections Acquired during the First Two Years at School The students were asked to consider why, if all children are to a greater or lesser extent exposed, some are much more seriously affected than others The students studied local school-attendance figures, school buildings, physical constitution, and other facets of the problem A member of the staff of the City Health Department, an otolaryngologist, and a specialist in social medicine came to the session and joined in the discussion

(iii) Family Problems and The Family Background in Pædiatrics are titles that have been chosen They provided an opportunity to study individual children against a difficult background and to allow us to introduce the students to the children's officer, almoners from other departments and members of the school medical and child-welfare services

Evening Sessions

Many of these sessions have now been held and I have found that it is particularly important when dealing with small groups of students to choose a subject that will interest all those who are on the firm at the time

(i) Neonatal and Infant Deaths have been studied, sometimes against an historical and geographical background and on other occasions dealing with local figures over a twelve-month period In the second case, deaths in the two maternity departments, in the wards, and those occurring in the city were investigated together with a special study (made with the help of the police surgeon) of sudden deaths in infancy It has been interesting to see how the different groups have tackled these problems and the ingenuity shown in collecting their data and arranging their work, one paper opened with the views of Tristram Shandy's father on the dangers of vertex delivery and another was purely factual and well illustrated by graphs

(ii) The Cerebrospinal Fluid gave the students an opportunity to study anatomy and physiology, the blood-brain barrier, and congenital abnormalities as well as the changes produced by infection, neoplasm, &c Cases from the wards were used in illustration

(iii) Infants admitted with acute respiratory disease were closely studied A detailed investigation was made of those who died, with a view to learning whether anything further could have been done, from the first sign of illness at home, to save these children's lives Incidence was plotted against temperature and humidity at the relevant time, the data having been obtained by one of the students from the School of Geography

(iv) Readmissions The students tried to discover why certain children came into hospital more than once They were asked to suggest what special steps could have been taken to help this particular group In the nicest possible way the omissions of the pædiatrician were brought home!

Other subjects have included The Forms of Mental Defect which may be Preventable or Treatable, The Purpuras, Some Preventable Conditions, and Ward Infections

Conclusions

I believe these sessions have been valuable in many ways On occasions they have not taken place because the students have been over-occupied by a special pathology examination or there have been absences due to illness Even more rarely, the group has appeared uninterested in pædiatrics and the teacher has, very temporarily, become discouraged and felt no inclination to put in the time and trouble necessary for a good meeting Perhaps not least of the advantages of an evening session is the contact between staff and students outside hospital These somewhat exhausting parties usually finish around midnight, washing beer glasses at the kitchen sink

My thanks are due to all those who have helped me and particularly to the students

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A TEACHING-ROOM ON THE WARD

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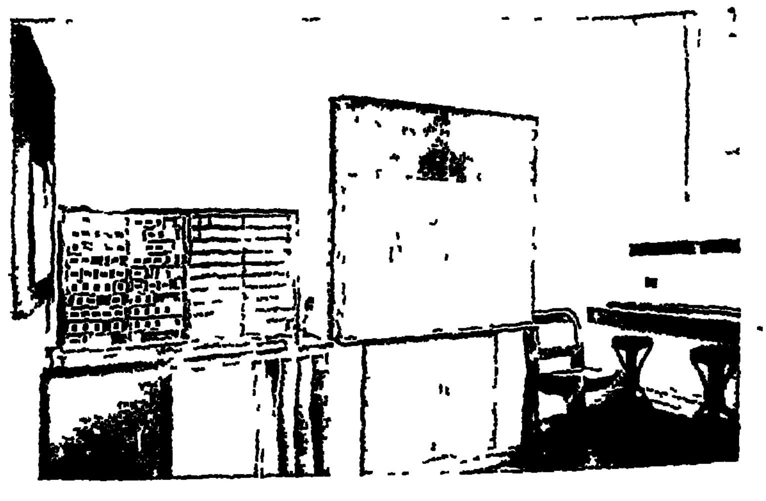
During the clinical years medical students spend much of their time in the hospital, and great stress is laid on teaching by the bedside For the most part there is no special provision for teaching in the wards, and teacher and students must fit in as best they can It is undesirable for a teaching session to be completed at the bedside, for the patient may be much alarmed by what is said or implied In practice it is customary for the clinic to move to the centre of the ward, to a corridor, or to an empty side-room before diagnosis, treatment, and prognosis are discussed

The gynæcological staff in the Royal Victoria Infirmary, Newcastle upon Tyne, have long felt the need for a permanent teaching-room on the ward In 1955, with the support of the teaching-hospital group and the University of Durham, it became possible to plan and equip a special room for this purpose The unit at that time was enlarged to 44 beds arranged in single and double rooms and small wards The teaching-room is situated centrally and is easily accessible from any part of the ward On the centre of the left-hand wall (see figure) is a large blackboard, which opens up to reveal a projection screen To one side of this blackboard is a cabinet with sliding frames and backlighting, used for storage of 450 colour transparencies, 2 in × 2 in Below the cabinet is a specially designed cupboard in which panel demonstrations are stored A bench runs round two of the other walls A sliding shelf extends 2 feet from the centre of the bench facing the



screen When needed, the projector sits on the shelf A table viewer is available, when in use it is placed on the bench, and six or eight students can look at the enlarged image

Discussion

University and hospital have combined to produce this teaching-room on the ward, and its many uses have justified the modest expenditure

Once the patient's history has been taken and any physical signs demonstrated, it is to everyone's advantage that discussion should take place elsewhere than at the bedside The patient is spared anxiety, teacher and students can speak freely There can be no privacy in the centre of the ward or in a corridor, in either situation interruption and disturbance are likely The teaching-room offers complete seclusion There are also advantages in having a selection of visual aids available on the ward

For example, one case of cervical erosion may be demonstrated to students in the ward, and then, from the collection of colour transparencies in the teaching room, they may be shown several other cases These benign cervical lesions can then be compared with malignant lesions of the cervix The transparencies can be viewed carefully and repeatedly, and in this way the student is likely to appreciate more clearly the differences between benign cervical erosion and early cancer of the cervix This use of the teaching-room gives added point to clinical teaching on the ward

At intervals, panel demonstrations are set up in the room and left for several days, so that students attached to the department can study them at leisure This form of teaching aid has already been described (Russell et al 1956)

Instruction in gynæcological histology is given once a week in the teaching-room, microscopes are set out on the benches for this class

It is not unusual to find rooms of this type in medical schools or in departmental headquarters, but much is lost by their distance from the ward When situated on the ward, a teaching-room such as I have described can make a significant contribution to the clinical teaching programme

I am indebted to Mr C J Duncan and Miss D Mustart for their help in designing and producing visual aids for use in the room

REFERENCE

Russell, J K, Duncan, C J, Mustart, D (1956) *Lancet*, ii, 383

ILLUSTRATION DISPLAY STAND

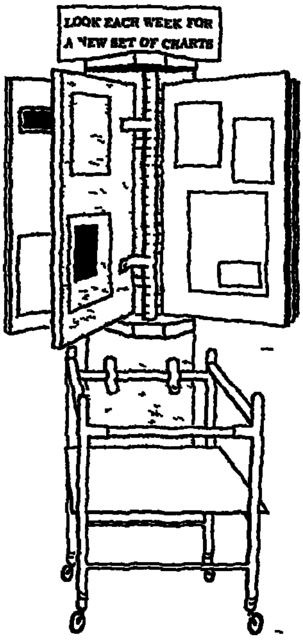
M C Joseph
M D Cantab, M R C P
ASSISTANT DIRECTOR

R C Mac Keith
D M Oxon, F R C P
PÆDIATRICIAN

DEPARTMENT OF CHILD HEALTH, GUY'S HOSPITAL, LONDON, S E 1

A stand for displaying pictures and charts has been in use as a teaching aid in the children's department at Guy's Hospital for the past two years

In basic design it resembles the leaved stands on which picture-postcards are displayed (see accompanying figure) It consists of eight square leaves of 'Essex' board type (58 cm × 58 cm × 0 7 cm) framed in wood. Each leaf is hinged on a central pillar mounted on a ward trolley 42 cm × 42 cm Each leaf is painted a different colour The upper glass shelf of the trolley has been removed, and the lower replaced by a sheet of 'Formica' as being more robust



The illustrations, mounted on light card, are secured by pins to both sides of the leaves Cards of any size up to the dimensions of the leaves can be used, and several pictures of different sizes can be put on the same leaf

A valuable feature of the stand is the ease with which several students or nurses can view the illustrations simultaneously Being mounted on a wheeled trolley, the whole stand can be easily moved to display the same or different sets of pictures elsewhere

A new set of pictures is put up each week, six sets being kept in the department in separate envelopes Each set includes pictures dealing with development, infant feeding, diseases, treatments, prophylaxis, and health education

The stand is usually kept in a large anteroom from which open the children's wards and operating-theatre, it is therefore seen by nurses, anæsthetists, and surgeons as well as by the medical students

The stand is easy and cheap to make, ours cost about £5

Our thanks are due to Mr E Smith and Mr F West, of the Medical School workshop, to Mr W P Bentley, of the works department, and to Miss P Carter, of the illustration department, Guy's Hospital Medical School

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Reviews of Books

For Future Doctors

Alan Gregg, M D Chicago University of Chicago Press London Cambridge University Press 1958 Pp 165 26s

In many countries medical education and research are becoming increasingly dependent on financial grants from various bodies and individuals From this situation has emerged a new figure in medical circles, the "professional philanthropic investigator". The late Dr Alan Gregg was such an investigator, and for thirty-seven years advised the medical-sciences division of the Rockefeller Foundation how its immense funds might best be dispensed This book contains the text of eleven addresses he delivered to medical schools or student bodies during that time One might be excused for surmising that, in his official capacity, he would have been sure of a hearty reception wherever he went But it is apparent from his lectures that, Foundation or no Foundation, his views merited very careful attention

He has devoted his chapter On Reading, not so much to advice on what to read, as on what to reject Dr Gregg felt that the medical student is at a disadvantage, compared with members of other faculties, when he is required to distinguish between a logical argument and an illogical one His course entails mastering so much factual information that his teachers spend all their time teaching him what to think, rather than how to think In consequence, many a student never learns to discriminate between praiseworthy books and articles, which advance his knowledge, and those which are badly written and confuse him (The sort that Lord Balfour, no doubt, had in mind when he spoke of "things that would have been clearer if they had not been explained") Dr Gregg lays down some criteria for recognising true worth and validity in medical argument, and he points out that many doctors, young and old, are sadly misled, in their reading and writing, through an ignorance of the laws of probability "One of the great needs of medicine, particularly for men in research work, is a course in evidence"

Dr Gregg's remarks have an international flavour and we hope they will continue to be widely studied on both sides of the Atlantic

Surgery in Infancy and Childhood

A Handbook for Medical Students and General Practitioners MATTHEW WHITE, M B, F R F P S, F R C S E, consultant surgeon, Royal Hospital for Sick Children, Glasgow, WALLACE M DENNISON, M D, F R F P S, F R C S E, Barclay lecturer in *surgery in relation to infancy and childhood*, University of Glasgow, and surgeon, Royal Hospital for Sick Children, Glasgow Edinburgh E & S Livingstone 1958 Pp 444 45*s*

THIS welcome book is a pioneer Its first intention is to introduce the senior student to the problems of surgery in infancy and childhood That it should come from Glasgow is indeed fitting, for the final-year student of that university has taken a ten-week course in the subject over the past quarter-century The authors are thus singularly fitted to judge the needs of these men

The book is easy reading and yet contains all the necessary detail Indeed, some may think it contains too much for the student The embryological diagrams and digressions are valuable because they illustrate the need for the children's surgeon to think as an applied embryologist—for example, in elucidating the malrotations But, for instance, a series of diagrams of the operative technique for the repair of a large omphalocele seems unnecessary, and the photograph of the sequelæ of a leopard's mauling contributes little The space devoted to cardiospasm seems excessive for a childhood rarity For rectal prolapse the usual advice to strap the buttocks together and "teach" defæcation lying on the side is given Surely this unpractical suggestion should disappear from future editions? But these are small matters in an unusually consistent book

The opening chapter recounts the special problems of surgery during the period of growth and development, and the physical and psychological importance of the timing of the procedures It is pleasing to see such subjects as the malar hæmatoma and adherent labia described and pictured These are the kind of minor conditions which can occasion great parental anxiety and which are passed over in most surgical texts

From this book the student will get a clear picture of the scope of pædiatric surgery General practitioners—and indeed surgeons and pædiatricians—will also find it a convenient resume of the subject

Bibliography of International Congresses on Medical Sciences

Editor W J BISHOP Council for International Organisation of Medical Sciences Oxford Blackwell 1958 Pp 238 25*s*

"THE purpose of the present list is to provide a guide to congress organisers, librarians, editors and others who wish to trace the published proceedings of medical congresses" it is not a complete record of international medical congresses but covers only those whose proceedings have been published The details of each are limited to subject, site, date, "bibliographical description", and languages Their alphabetical arrangement, though it has its convenience, presents certain difficulties, and even with the help of the index it may not always be easy to find what is sought But the book contains information which, when one needs it, may be hard to get from other sources

John Wesley among the Physicians

A WESLEY HILL, B A, M B London Epworth Press 1958 Pp 135 10*s* *6d*

THIS interesting and well-written book is concerned to bring to the notice of a wider public the activities of John Wesley, physician Dr Hill gives extensive excerpts from Wesley's three medical works, *Primitive physick*, *The family physician extracted from Dr Tissot*, and *The desideratum, or electricity made plain and useful* The practice of other physicians is mentioned to bring into relief Wesley's simpler and often less harmful approach to human suffering Dr Hill's criticism that "Wesley in his enthusiasm may have optimistically over-rated many of his results" applies also in some measure to his own evaluation of his fascinating subject For instance, it is doubtful whether his thesis that Wesley made "some attempt at liberating medicine from these [medieval] theoretical coils and at setting it upon an experimental basis" can be maintained The more correct interpretation seems to be that he was concerned to better the physical health of the masses by providing rules of hygiene and simple and cheap remedies within the reach of all—hence his enthusiasm for the new electrical treatment These were important contributions to 18th-century medicine Most striking, in retrospect, is the extent to which Wesley realised the importance in disease of psychological factors which orthodox physicians tended to overlook in practice if not in theory

The Human Hand

GEZA REVESZ Translated by JOHN COHEN London Routledge & Kegan Paul 1958 Pp 138 31*s*

THE late Professor Revesz, of Amsterdam, devoted much study to language, tactile perception, and the psychology of the blind and the deaf It was therefore easy for him to write a book on the hand as the organ of haptic sensation and the agent of much non-oral communication The result is a discursive essay, it is reinforced by footnotes referring to technical articles, but in the main it avoids detail and aims at reminding the reader rather than instructing him It can be regarded as a sister-piece to Wood Jones' anatomical study of the human hand and, though less original than that work, resembles it in its emphasis on the importance of the hand in man's development and achievements

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Modern Trends in Anæsthesia (London Butterworth 1958 Pp 331 67*s* *6d*)—This volume, edited by Dr Frankis Evans and Dr Cecil Gray, marks a period of consolidation in anæsthesia, which its inquiring and scientific approach well illustrates By careful presentation of established physiological and pharmacological facts, the contributors contrive an excellent picture of the implications of anæsthesia rather than of its practical application The new knowledge of recent years is well reviewed, the direction in which the specialty is moving is ably illustrated, and those aspects are indicated where further research and study are needed A large part of the book deals with the chemistry and mode of action of drugs, but their place in clinical practice is not forgotten, and there are chapters on hypothermia, cardiorespiratory pumps, pulmonary ventilation, hypnosis, and disorders of the respiratory system This is a most useful addition to the library of anæsthesia, which is enhanced by the authors' liberal choice of contributors The mutual interests of anæsthesia and other branches of medicine are well represented by authorities both within and without the specialty, and recent developments in Scandinavia and America are ably described by experts from those countries

Infant Feeding and Feeding Difficulties (3rd ed London J & A Churchill 1958 Pp 293 16*s*)—For this edition the book by Dr Philip Evans and Dr Ronald Mac Keith has been carefully brought up to date It is very comprehensive and includes procedures likely to be used only by resident staff The bias in favour of breast-feeding is reflected in the fact that over half the pages are devoted to its problems

THE LANCET

LONDON 30 AUGUST 1958

Education *v.* The Curriculum

EARLIER this year TANNER[1] outlined a reorientation of preclinical studies which would, in his view, make them more appropriate than they now are to the practice of medicine, at present largely concerned with applied human biology. At that time we forecast[2] small likelihood of such ideas being translated into action in British schools. The powers of resistance to change include the fear of giving up what was once good, in favour of the new and unproven, and in the federation of departments which makes a medical school, that fear can easily be exploited by any unit which suspects that its own interests can best be served by adherence to the status quo. But we added, " if all the older schools are tied to their dead past the same cannot be said of new schools, such as that of Western Australia ", and we are very glad, therefore, that Prof DAVID SINCLAIR has written the article on p 430 describing the curriculum which, it has been agreed, shall at the moment be used in Perth. The planning of the early years suggests that the aim accords to some extent with that of TANNER. The actual programme, however, also reflects many local and, it is to be hoped, temporary obstacles. One of these at present means that the first year is spent in isolated study of " premedical " subjects. The second year, on the other hand, will consist of a coordinated course in human biology, with at its end a single examination which should act as a stimulus to the student to integrate his studies of anatomy and physiology. Dissection of the whole body will be required and will be carried out under the pressure of the traditional viva system until the professional examination in topographical anatomy at the end of the second term of the third year. A term later the student will take one examination in biochemistry and another in " physiology and the general principles of pathology (with one question on psychology) " We hope that before long circumstances will allow these two examinations to be fused, so that the student may be encouraged to link the general principles of pathology with physiology, psychology, and biochemistry (and even anatomy)—as obviously he must.

SINCLAIR points out that although the plan he describes has been agreed to by all his colleagues some of them would place a different emphasis on the description. This no doubt would apply to the clinical part of the curriculum, in which no mention is made of that exceptionally important though technical part of medical education—the introduction to clinical method. The arrangement of the clinical years is, however, of such simplicity that at least it cannot be criticised for being diffuse. A first year in the wards (during the first half of which the course and examinations in pathology will be completed) should give the student that advantage of long-continued practice in clinical method which has been such a good feature of the traditional British training. A second year consisting of four months' obstetrics and gynæcology, four months' pædiatrics, and four months' experience of specialties (with a carefully coordinated course in preventive medicine) indicates that the University of Western Australia is at the outset keen to achieve that sense of proportion, in regard to specialisation in undergraduate education, which characterises the best American schools. A final year " relatively free from formal classes " in which the student may gain experience and integrate his knowledge is, of course, something to which almost every British school is vainly trying to return.

As HALE HAM[3] has said, " The curriculum is the course through which the student travels, it is a definition of limitations as well as opportunity " It closely resembles a railway guide which shows the expected times of arrival and departure, occasionally explains the local reasons for the route taken, and briefly indicates the main features of interest in each stopping-place. It does not state the degree of efficiency of the organisation, nor reveal its standards or those of its employees. Sometimes its avowal of close concern with the problems of the individual should not be taken too literally. Unfortunately in many medical schools in this country there are railway-guide teachers who still think of medical education primarily in terms of the curriculum. Unless a suggested improvement or reorientation is expressed in time-table form it seems to them to be hopelessly vague and diffuse—yet it cannot be translated into such form except by themselves in collaboration with their colleagues. Thus, old curricula remain, annually becoming structurally more " concrete " but functionally less successful and some schools wait on, in agitated depression, for ready-made " concrete plans " which will never come. For this reason, we said[2] " to break the mould of the existing curriculum it may be necessary to start in Britain a new medical school "

As one means of solving our problems SCOTT[4] pleaded for restoration of the art of " great teaching " to its proper place. But the " great " teachers were largely engaged in teaching what was known, while we are now equally concerned with teaching the best attitude to what is not yet known. " He teaches best," said ALAN GREGG in 1953,[5] " who shows his students how to learn not what to think in 1953, but how to think and how to learn to think in that long stretch of days (ahead) till, let us say, the year 2000 " We agree, however, with SCOTT and with WILSON[6] that there is a great need for " teachers who take their responsibility as teachers as seriously as they take their research work or their clinical duties " We are particularly impressed, therefore, with the principles which, as SINCLAIR records, were kept in mind during the planning of the Perth curriculum "A series of weekly lunch-time meetings was instituted among the professors, and it is proposed to continue this most valuable practice indefinitely." "The second principle was that the details of time-table arrangements or teaching methods must never obscure the all-important attitudes of both teachers and taught towards the process of becoming a doctor"

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[1] Tanner J M *Lancet*, 1958, i 1185
[2] Ibid p 1213
[3] Hale Ham T An Experiment in Medical Education at Western Reserve University p 13 New York, 1954
[4] Scott J H *Lancet* 1958, i 1334
[5] Gregg, A For Future Doctors, p 50 Chicago, 1957
[6] Wilson, R. R. *Lancet*, July 5, 1958, p 45

This augurs well for the future of Perth Meanwhile, in this country, our best hope seems to lie in the Association for the Study of Medical Education,[7] which will hold its first conference [8] on Sept 25 and 26 If it can draw together all the interested teachers from all disciplines and all schools, it will not only provide them with mutual strength and encouragement but will also enable them to work together to increase our knowledge of education The stimulus to progress thereby generated cannot be ignored it can produce that factual evidence of present weakness, and of the results of change, which alone will convince the faint-hearted, and the too easily satisfied, that change has to be made

Tropical Practice

MEDICINE in tropical climates has always been a challenging affair, and its enormous problems have attracted outstanding men Now that the perils of monsoon and insect have to some extent receded, doctors in the tropics are looking at matters which had previously been masked by the daily drama and, perhaps, by the traditional approach to scientific medicine From her wide experience, Dr CICELY WILLIAMS [9] believes that training in pædiatrics for the tropics is not as good as it should be—and we agree [10] Now, in this issue, Dr JOHN WRIGHT puts forward some good ideas for overcoming present deficiencies and for helping the tropical neophyte With increasing specialisation and complexity in Western medicine, training needs for the "home front" and for the tropics are always diverging The doctor in veldt or jungle has no second opinion, and to "pass the buck" may involve a long journey by bullock cart and an expense that the patient's family cannot afford The doctor's daily tasks may include drawing a tooth, removing a uterus, taking an X-ray (if he is lucky enough to have a machine), and fitting a new half-shaft to the hospital van-cum-ambulance Medicine of this calibre demands high skill and considerable mental stability

Among his proposals for meeting this challenge, Dr WRIGHT's most interesting suggestion is a year's "internship" in a teaching hospital at the place where a doctor intends to work This seems such good sense that we wonder why it was not introduced long ago there are still too few suitable institutions, of course, and perhaps the small number of doctors has made the "waste" of a year impossible But tropical medicine is not just a specialty, it is a complex of specialties, and the doctor in India will find himself dealing with a different set of problems in different circumstances and in a different culture from his colleague, say, in Africa or British Guiana—and therein lies the difficulty of teaching the subject thousands of miles from where the students will finally work It is a good idea, too, to ask tropical practitioners on furlough to help home-leave is still, happily, on the grand scale, and many of them would be pleased to share their experiences and earn a little extra money

Dr WRIGHT treads on emotionally insecure ground when he suggests that new countries should scale down the training of students to methods they can afford, but, as he points out, what is sauce for the British goose is not necessarily sauce for the tropical gander, and medical practice will improve by adaptation to local circumstances Dr WILLIAMS thought it wrong for developing countries to put emphasis on large Western-style institutions, and we believe that Western experts do a disservice if they encourage such Governments to start costly ventures of uncertain value Likewise, as Dr JOHN B GRANT has insisted,[11] the undergraduate medical curriculum in the tropics should be devised, not to reflect curricula in the U S A or the United Kingdom, but to train an "undifferentiated physician", competent to undertake general practice in his own community Obscure investigations, all-day operations, complicated treatments may be out of perspective when the average age of death is in the thirties and infant mortality is twenty times as great as in Britain This is not to say that research has no place in the tropics, but it should be devoted to the vast unsolved problems of epidemiology and nutrition and to the relationship of disease to the wide cultural differences throughout the world Many Western riddles might be solved if we knew the answers to the sort of questions that abound here Why is appendicitis so rare in some primitive rural communities? Why is disseminated sclerosis almost never seen in India? Why is syphilis so widespread in the tropics, yet affection of the central nervous system so rare? If the difference is due to "autotherapy" from attacks of malaria, does the pattern hold for malaria-immune hill areas? Facts emerging from careful work in the tropics could radically alter ways of life in many other countries

How should the doctor fit into this changing pattern of tropical practice? Hitherto, effort has centred round isolated overworked Government or mission hospitals, and it is tempting to follow a more thorough version of this plan But large-scale curative and preventive measures, though very necessary, are of slight value when unsupported by coordinated development projects touching many aspects of life—economic, eugenic, educational, technical, domestic, and (many would add) religious Such plans are proceeding in India on a heroic scale,[12] and the experience they are providing will be of the utmost interest to all who work in deprived countries In this scene, the "greater medical profession" includes experts in many social and technical subjects, and the doctor is little fitted by training for such comprehensive collaboration—another aspect, perhaps, which could be approached during a " tropical internship "

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[7] *ibid* 1958, i 1261

[8] *ibid* Aug 2, 1958, p 273

[9] Williams, C D *ibid*, 1958, i 863 919

[10] *ibid* p 951

[11] See *ibid*, p 1009

[12] *ibid* 1956, i, 491

Learning

What is to be readily remembered must be taught without tears this moral is suggested by some recent comments of Dr Ritchie Russell [1] [2] on the physiology of learning and memory As befits a clinical neurologist, he has concerned himself primarily with human learning and he has emphasised the importance of encouraging in all educational endeavours " personal feelings of the optimal type ", since, as he says, " every memory seems to carry its own personal reaction or feeling " He also discusses the problem of innate versus acquired intellectual ability, and again his conclusion is encouraging in regard to the potential value of efficient instruction, for he leaves open the question of whether outstanding mental capacity is predominantly innate or acquired Educationists may find further incentive to their efforts in the work of Newman et al ,[3] who studied the relative contributions of heredity and environment in determining the performance in intelligence tests of identical twins Results suggested that the scores achieved by identical twins in the Stanford test are much affected by environment, since the divergence between these individuals, whose genetic make-up may be assumed to be very similar, is much greater when the siblings are separately reared than when they share a common post-natal background

Of course there are limits to what can be achieved by any educational method, and some anatomical observations are relevant Extremes of underdevelopment amounting to the congenital absence of the physical apparatus required for intricate mental processes are seen in anencephaly and severe porencephaly, and also in the so-far irreversible effects of an unfavourable " internal environment " during certain vital stages of cerebral maturation, as in the untreated cretin Apart from these, however, there is considerable variation of brain size, even in relation to body size, within the human race, and on the whole there seems to be a poor correlation between cerebral mass and intellectual brilliance It is true that of the (presumably complete) brains the weights of which were recorded by Lassek,[4] the smallest, which weighed 289 g , belonged to an adult mental defective, and the largest, of 2012 g , belonged to the celebrated Russian writer, Turgenev Nevertheless one quite normal man had a brain of 650 g , and the only anatomist in Lassek's list contributed merely 1198 g of cerebral tissue The possessor of the 650 g brain had a body-weight of 66 kg , which gives a brain to body-weight ratio of 1 105 as compared with the average human figure of 1 44 (The marmoset, incidentally, has a ratio of 1 27 and the whale of 1 8500) To be set against such static morphological data are the more dynamic observations on changes of weight and structure with age The relatively rapid increase in size of the human brain in the early years of life results in roughly a doubling of its weight between birth and the end of the first year, thereafter its mass increases at a diminishing rate until the age of about 25 More interesting perhaps are the changes after the 25th year Between the ages of 20 and 80 the brain loses some 10% of its weight, and Burns [5] estimates that during every day of a man's adult life several thousand grey cells must die It is obvious from a superficial consideration of localising signs in nervous diseases that adult cerebral neurones are not mutually equivalent, but the depopulation of the cerebrum on this scale is a challenging observation to those who have passed their second decade of life

In the experimental study of learning, the researches of Pavlov [6] on conditioned reflexes are fundamental work He demonstrated the possibility of associating a response such as salivation, which is a natural consequence of eating, with an unnatural stimulus such as the shining of a light Most of Pavlov's experiments were carried out upon dogs, which " learned " the new association after some twenty or so repetitions of the two stimuli, the natural and the unnatural, in combination It has since been shown by Boycott and Young [7] that a much more primitive creature, the octopus, is capable of being trained in a similar way Yet it is a far cry from the establishment of such relatively simple trains of association, based on repeated exposure to the same experience, to the capacity for rapid assimilation of knowledge displayed by such historic figures as Lord Macaulay, who, it seems, would take in at a glance long passages of print which he could later repeat almost verbatim, or Dr Samuel Johnson who was said never to have forgotten anything he read Conditioned reflexes of the simple pavlovian type can apparently be established in decorticate dogs, but more complicated reflexes which involve the addition to the response of a second normally " voluntary " action, such as movement of a limb, are attainable, in dogs, only in the presence of the cerebral cortex In rats, however, there is evidence that " learnt " reactions to visual stimuli can be effected through subcortical mechanisms after—but only after—the visual cortex has been removed It seems clear from the work of the ethologists that in certain animals remarkably complex patterns of behaviour must be regarded as innate or instinctive Such patterns can be evoked by rather simple triggers once the natural triggers are identified Thus, Tinbergen [8] has provoked aggressive conduct in the stickleback using a suitably coloured dummy, and Lorenz,[9] after recognising and imitating the essential features of maternal behaviour in ducks, was able to impose himself successfully as a mother substitute upon a brood of ducklings which reacted almost as demonstratively to him as to their natural matriarch It is true that in these instances the natural stimulus was mimicked, but it seems likely that artificial stimuli might be superimposed by appropriate pavlovian conditioning.

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[1] Russell, W R *Proc R Soc Med* 1958, 51, 9 See leading article, *Lancet* 1957 ii 729

[2] Russell, W R The Physiology of Learning Royal College of Physicians, Edinburgh, 1957

[3] Newman, H H , Freeman, F N Holzinger, K J Twins a Study of Heredity and Environment Chicago, 1937

[4] Lassek, A M The Human Brain Springfield, Ill , 1957

[5] Burns, B D The Mammalian Cerebral Cortex London, 1958

[6] Pavlov, I P Conditioned Reflexes London, 1927

[7] Boycott, B B , Young, J Z *Symp Soc exp Biol* 1950, 4, 432

[8] Tinbergen, N The Study of Instinct Oxford, 1957

[9] Lorenz, K Z King Solomon's Ring London, 1957

On the other hand, animals can acquire high competence in certain tricks, and dogs, parrots, and circus animals have made substantial reputations in this way Stereotyped exercises of this general kind have been much used in the study of learning, particularly in rats and monkeys, and it is tempting to physiologists to interpret such acquired skills, which improve with practice, as being mediated by the development of preferentially excitable nervous links connecting the receptor and effector organs, by analogy with the heightening of excitability in spinal neurones which, as shown by ECCLES and MCINTYRE,[10] can be induced under suitably chosen conditions The analogy is imperfect, however, and any simple concept of a unique nervous pathway underlying such learnt skills is made unacceptable by the experiments of LASHLEY[11] He showed by excision of different portions of the cerebral cortex of trained animals that the postoperative disability in performance of the learnt tasks was proportional to the extent rather than the location of the cortical damage This conclusion is rather at variance with some clinical data relating loss of memory to localised cerebral lesions Thus, at first sight it appears to conflict with PENFIELD's[12] finding that quite detailed and reproducible memories can be elicited by stimulation at operation of a very small area of human cerebral cortex But PENFIELD himself is inclined to interpret his results in terms of activation of some region, other than the stimulated cortex, which is the location of what he calls the "actual ganglionic patterns of experience"

The psychological approach to the elucidation of learning processes has evoked many theories of learning (HILGARD[13] lists ten) Certainly, any comprehensive theory should take into account information obtained by psychological techniques of investigation, and every satisfactory psychological theory of learning should have an acceptable physiological substratum, since, as LORENZ[14] has emphasised, there can be no psychological process which does not have its physiological correlate

In the understanding of the learning process much remains to be explored and hence many advances are to be expected That should prove a happy augury for those embarking on the learning of physiology—provided active curiosity rather than passive receptivity is to qualify as an "optimal feeling" in Dr RITCHIE RUSSELL's sense of the term

The Student Apprentice

THE rise of the great teaching institutions based on universities and hospitals saw the decline of the apprenticeship system The humanity of medicine may have suffered from this change, for institutional teaching cannot replace the personal understanding given by a sympathetic teacher to one or two disciples The swing of the pendulum towards institutional teaching was the inevitable result of scientific advances, but the return swing is equally inevitable and we can already detect its beginning

Since its foundation the College of General Practitioners has pointed out that, though disease has for generations received almost exclusive attention in the formal medical curriculum, the patient is equally worthy of the consideration and respect of the medical student. Between the wars it was exceptional for the student to meet the general practitioner and his work, though in Edinburgh students could include dispensary practice in their experience The belief may have been that general practice need not be taught because it was no more than the application in independent practice of all the knowledge the student had gained in hospital Such a view could well take root in the corporate mind of a congeries of specialist teachers, none having been in general practice Or it may have been argued that an activity of so wide a scope could not be taught, and that any attempt to teach it was doomed to failure This view has not been accepted by the College of General Practitioners, whose undergraduate education committee has lately published[1] a summary of its activities and a statement of its policy—a document which will be welcomed by deans of medical schools, to whom it is primarily addressed The structure of the college is such that, with few exceptions, each of its faculties has, in its region, a university with a medical school, and all encouragement is given to the university to seek the help of the undergraduate education committee of the faculty It is not the function of the college to proffer unsolicited advice, but these committees can work closely and profitably with undergraduate deans The college believes that the benefits of an early introduction to general practice (such as are described by Mr BERZON on p 441) should not be confined to those who intend to make this their vocation, and that those who look towards a consultant career should certainly share them Some, even within the universities, would go further and say that no aspirant to a specialty of any kind should be allowed to forgo such an introduction

In support of the undergraduate teaching schemes which are being increasingly adopted by the medical schools themselves,[2] the college offers to arrange attachment of final-year students to general practitioners on an undergraduate teaching register This register is based on a questionary circulated to members of the college in 1957, and contains the names and addresses, with details of qualifications and experience, of over 1000 general practitioners who have indicated their willingness to accept students in their practices Deans of the medical schools will want to know that this register is to be kept up to date Many of those named in it will already be known to the universities as teachers, and may already be taking students The remainder, by inclusion in the college's list, carry by implication the college's recommendation Willingness to accept a student in a practice usually presupposes high standards —at least in the eyes of the doctor himself—but from among a list of volunteers there may be some less suitable than others The undergraduate education committee of the college will do well to scrutinise future applications from doctors to join the register, to ensure that those admitted are able to maintain standards that will satisfy a critical and possibly sceptical dean

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[10] Eccles, J C, McIntyre, A K *J Physiol* 1953 121, 492
[11] Lashley, K S *Symp Soc exp Biol* 1950, 4, 454
[12] Penfield, W The Excitable Cortex in Conscious Man Liverpool, 1958
[13] Hilgard E R Theories of Learning New York, 1956
[14] Lorenz, K Z *Symp Soc exp Biol* 1950, 4, 221

[1] On Undergraduate Education and the General Practitioner Supplement to the *Journal of the College of General Practitioners*, August, 1958, vol 1, no 3
[2] *Lancet*, 1957, ii, 415

How far student teaching in the home and in the surgery can be supported by general-practitioner teaching in the wards and lecture-rooms remains to be seen And there is also the possibility of extending present arrangements to give the student much greater responsibility (as is done in Boston under the scheme described by Mr HASS on p 442) Medical schools and universities will continue to give thought to such developments, for, as Dr LOGAN says earlier in this issue, "to farm students out to general practitioners for short periods is hardly enough" If it is accepted, however, that the general practitioner can help to draw many divergent specialties together and present them as a coherent whole to the medical student, then a department of general practice in each university is the next logical step Such departments could, among other things, undertake the research into general practice that Dr LOGAN asks for

Annotations

SOCIOLOGY OF MEDICAL EDUCATION

A STUDY of the sociology of medical education was begun some years ago by the Bureau of Applied Social Research of Columbia University (with the aid of the Commonwealth Foundation), and in this inquiry students and staff in the medical schools of Cornell University, the University of Pennsylvania, and Western Reserve University collaborated A first set of reports has been published under the title *The Student Physician*[1] and makes a book unique in the literature of medical education It is not concerned with "what is being taught, what should be taught and how it might most effectively be taught", but with the process of education in the medical school, and "the ways in which its social structure, like that of other organisations, largely forms the behaviour of its members and so affects the makings of the medical man" The aim has been to discover to what extent and through what processes the medical school shapes the professional self of the student, so that he comes "to think, feel and act like a doctor" Prof Robert Merton, of Columbia, who has been mainly responsible for directing the investigation, writes "Students learn not only from precept, or even from deliberate example, they also learn—and it may often be, most enduringly learn—from sustained involvement in that society of medical staff, fellow students and patients which makes up the medical school as a social organisation" It is the basic values of their professional life which are learnt in this way

This work has produced a large mass of information on a subject never previously investigated Rightly, therefore, no attempt has been made to give significance to any of it Nor can any of it be lifted from its American context and applied to British students and schools This pioneer enterprise, however, is a stimulus from which many can profit by examining its methods, even though in Professor Merton's words they "do not meet the strict requirements of experimental enquiry" They are "more nearly like methodical studies in natural history and ecology than like laboratory experiments," but they are far removed from casual impressions

In this country it is now accepted that medical education must be studied In medicine we are committed to the reduction of empiricism by scientific inquiry, and few now persist in the view that a similar outlook is inappropriate to medical education This dwindling opposition may itself need methodical inquiry, for "institutional procedures, once functional for their time and place, engage the loyalties of men involved in them These men, able to point to the undoubted accomplishments of the past and confident that their motives are above suspicion, find new arrangements unsettling and excessively unsure When the relative merits of competing alternatives are difficult to demonstrate, as they commonly are in establishing or modifying social institutions, the resistance to change is all the more intense" This resistance can be broken down only by increasing our knowledge of the processes of medical education.

The value of *The Student Physician* lies not in its information about the reactions of American students but in its description of the application of sociological research to education It illustrates how this newest method of inquiry can reveal and liberate the traditions of medicine as a force which can powerfully augment appropriate changes in medical education For "in Medicine, the great tradition is typically that associated with celebrated physicians of the past, with those who have shown a capacity to move forward when most of their colleagues were satisfied to let things remain as they were" We can recollect the words of John Morgan, written in 1765 and quoted in this book "the longer we follow any faulty system, the more difficult we find the task to break through the shackles of it, even when it enslaves us to our greatest detriment"

TEXTBOOKS A NEW STYLE?

ON trial for making a bonfire of the books of ancient scholars, Paracelsus called them a pack of lies, but if he had still been at his burning today he could hardly have made that an excuse for consigning the modern medical textbook to the flames It is not in their veracity but in their influence on the students' sense of proportion that some undergraduate textbooks seem to err The practice of medicine and surgery is still overwhelmingly based on informed guesswork, on an appreciation of probabilities The experienced doctor's greatest asset (what strikes his mystified juniors as his clinical "flair") is his sense of relative frequencies It is a sense that grows slowly, and it is retarded by the too easily acquired habit of thinking in terms of lists And lists are too prominent in many textbooks One or two skilful writers have been able to convey that all items on their lists do not have the same value, but that is an unusual quality, and it is the list which encourages the student to think of Whipple's disease before appendicitis and of lymphogranuloma inguinale before inguinal hernia We might go so far as to say that the undergraduate textbook which claims to be "comprehensive " should have this claim thoroughly investigated· only after it has been found correct should it be destroyed

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[1] The Student Physician Edited by ROBERT K MERTON, GEORGE READER, and PATRICIA L KENDALL A Commonwealth Fund Book Cambridge, Mass Harvard University Press London Oxford University Press 1957 Pp 360 40s

While similarly engaged last year [1] in the popular sport of belabouring the textbook, we suggested that there was a place for the book which made no claim to completeness but described essentials And we wondered whether a publisher would care to issue a cheaper " utility " edition of a textbook to compare its sales with those of the standard edition We are glad to welcome, therefore, *An Introduction to Surgery*,[2] edited by Mr David Patey, and published (in two styles of binding) by Lloyd-Luke Mr Patey and his colleagues introduce surgery without tears and with many positive merits Among the pitfalls they have avoided there are the 1000 and more pages which the book does *not* contain it has now been proved that 224 pages of carefully selected text can suffice for an introduction to surgery Almost half the book is devoted to general principles and not only the familiar but glimpses of the unknown beyond the limits of present knowledge The local reactions to injury are divided into intracellular and extracellular " The intracellular reactions are obviously of fundamental importance, but unfortunately we know very little about them At present, therefore, we can only note their potential importance " The temptation to include here some insignificant detail of the intracellular reaction about which something *is* known must have been strong The second section deals with methods of examination it is no less good, merely more conventional Some practical procedures are then described, and finally an excellent glossary will be a boon to students who have allowed the time when elementary questions can be asked without embarrassment to slip by without asking them Our only fear is that the book may prove so valuable that students will want to possess it in the more robust binding, so that the result of the two-binding experiment may be misleading

EPONYMS IN MEDICINE

THE clinical teacher who asks his class to write down the surnames of the men who described Colles' fracture, Pott's paraplegia, and Perthes' disease is likely to be greeted with exclamations of derision But there is a deceptive simplicity about the question, and experience has shown that an inquisitor who receives even one paper with all three names faultlessly spelt can pride himself on having a class of more than average alertness—or one (dare we hope) that reads *The Lancet* with commendable diligence

The creased brows and the erratic guesses about the position of the apostrophes may prompt some thoughts upon the advisability of using eponyms at all in modern medicine Some there are which will never be supplanted, by reason of the admirable precision, and the enduring style, of those who created them Hippocrates, for instance, describing the " sharp nose, hollow eyes and collapsed temples " of such ominous significance in acute infections, or Kussmaul with his " stuporous condition and the great loud breathing " Others will endure, if only because their use saves so much time in writing histories (Weber-Christian disease is, admittedly, not an entity which is diagnosed every day of the week, but when it is encountered it is more easily described as such than as " relapsing febrile nodular non-suppurative panniculitis ") ·

It is given to few men to describe a syndrome so completely that none of their colleagues can subsequently add anything to their work And when their colleagues do so, that student's nightmare, the hyphenated eponym, is likely to result In a comprehensive and erudite article, Shapiro [1] has lately discussed this aspect of medical terminology and its multiple incongruities Sometimes, and most logically, a hyphen joins the names of two workers who described a disease simultaneously—as did Morquio and Brailsford, writing of their osteodystrophy (The Montevidean wrote in a French journal, the Englishman in an American one, but both papers were published in 1929) On the other hand, nineteen years separated Stokes' description of " repeated cerebral attacks " from that by his colleague, Adams, who succeeded him to the same professorial chair in Dublin

" Occasionally, the hyphens become multiple, more years pass, and others act as midwives-in-eponymy " Shapiro cites the case of the Laurence-Moon-Biedl syndrome, and says that " to be just to all involved, this familial idiocy should be idiotically designated the syndrome of Laurence-Moon-Bardet-Biedl-Solis-Cohen-Weiss " There is one further pitfall about hyphens their use does not always indicate more than one author Krafft-Ebing, Brown-Séquard, and Albers-Schonberg were individuals, and not limited companies So were Austin Flint, Argyll Robertson, and Bence Jones—but *their* shades would not be gratified by hyphenation

One field of eponymous fame remains which few will dispute, and to which none will aspire If a man not only describes a disease for the first time but also does so from his personal experience, it is hard to contend his claim to have his name associated with it thenceforward Julius Thomsen has such a claim, for, though Leyden had written of amyotonia congenita two years earlier, Thomsen's description of five cases, published in 1876, has endured because the patients were himself and his four sons Similarly, Hillard's lupus stands uniquely in the name-strewn battlefield of dermatological nosology And whoever talks of a rickettsial infection pays tribute to an investigator who died of one in Mexico (On the other hand, contrary to the legend perpetuated in many histories, Percivall Pott did not sustain a fracture-dislocation of his ankle)

Despite all the contention their use involves (and all the grey hairs they bring to editors and type-setters), these titles cannot lightly be discarded They are part of the living tradition of medicine But when they are used, contributors and editors must strive to ensure that they are placed in a correct context and accurately rendered It is a poor act of homage that spells a man's title wrongly, or ascribes to him a different condition from that he described For how often must such thoughtlessness cause some great forebear of medicine to stir restlessly in his grave and exclaim, with poor Hamlet, " O good Horatio, what a wounded name, things standing thus unknown, shall live behind me! "

Dr W S C COPEMAN has been elected master of the Society of Apothecaries of London

Dr C C UNGLEY, physician to the Royal Victoria Infirmary, Newcastle upon Tyne, died on Aug 21 at the age of 55

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[1] *Lancet*, 1957, ii, 416

[2] An Introduction to Surgery Edited by DAVID PATEY, M S , F R C S , surgeon The Middlesex Hospital, London, and director of surgical studies The Middlesex Hospital Medical School London Lloyd-Luke 1958 Pp 225 Standard edition 17*s* 6*d* students edition 9*s* 6*d*

[1] Shapiro, E. *Arch intern Med* 1958, 101, 662

The Wider World

EDUCATION FOR THE TROPICS

JOHN WRIGHT
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ILESHA, WESTERN NIGERIA

> "We should ask ourselves from time to time whether we are giving these friends from abroad what they need, and whether we are giving it well enough." [1]

IN her excellent Milroy lectures,[2] Dr Cicely Williams touched upon some of the difficulties which stand in the way of successfully developing health services in the tropics, and discussed the adjustments which clinicians must make when they begin to practise in such countries.

When one steps aside from the County Ground of our own sophisticated medical service on to the Village Green of tropical practice, the truth of what she has written is all too evident, and its relevance is undeniable. What are at present "underdeveloped areas" will, within a generation or two, have an incalculable impact on the rest of the world, and the contribution which Western culture can make now to their health and development will have an equally great effect in moulding their future attitudes to us. To put it at its lowest, and without "taking an over rosy view of the sociological importance of doctors", the problems of rural health in the tropics are not ones which, in our own long-term interests, we can afford to be complacent about. They have about them an urgency which we, in our society, find hard to appreciate.

Certainly a real pride is permissible in the contributions which Britain has made, particularly in the last half-century, to the health of such underdeveloped countries. No-one can belittle the achievements of epidemic control, or the single-minded enthusiasm and selfless energy that has gone into them. Even so, our medical practice in the tropics has often been a matter in the past of the "microscope, the pill, and the injection", and we have tried sometimes to impose on developing tropical countries our own particular pattern of medical practice, sidestepping all the social background which the latter implies. Many British doctors, trained in British schools and set in the tropics, would confess at least to occasional doubts as to whether they were achieving anything solid, working on the pattern of English practice. In his first vivid impressions, professional life to him is too much like the treadmill: on the one hand, the body of disease is overwhelming, and the mortality (especially among the very young) is fantastic; on the other hand, the economic and technical resources to which he has access are desperately limited, and practice is constantly walled about with a social heritage he does not understand and cannot counter.

But such doubts are soon cushioned. It cannot be otherwise when each working day starts at 8 A.M., finishes 10, 12, or 14 hours later, confronts the doctor with patients in hundreds rather than dozens, and showers a kaleidoscopic variety of disease on him such as he has never had to tackle before. It is not difficult to understand how easily he comes to regard his hospital practice as his raison-d'être, and has few energies left for the wider view.

This is, moreover, an attitude in which he has been implicitly encouraged during his student or postgraduate days in England. His concern is sickness, not health, his duty not prevention but cure, and he has been encouraged to believe that the more competent his judgment grows the more restricted in range it must necessarily become. Striving for ever-increasing technical mastery of his own specialty, he seeks (quite rightly) the advice of specialists outside his own contracting field more and more. His eyes become turned to the minutiæ and he becomes more and more concerned with the technical intricacies of his own subject.

Out of this background, implied or developed, he is lifted, set down in tropical practice, and expected to be able to survey the needs of rural health successfully. To say the least it is an ill preparation that he has been given.

At the core of the situation, therefore, lies the problem of medical education—of how the present education of doctors for the tropics can be so altered as to provide both European and African doctors who are able to work more efficiently to their needs. And if it seems presumptuous for one who has never worked in a tropical teaching centre to reflect on medical education the only justification is that at least he has done so from a rural hospital on the Village Green.

The Village Green

This particular village green lies in a belt of tropical forest some 10° north of the equator. Its thirty acres are set on the top of some rising ground at the edge of a town of some 75,000 people. As in many of the bigger pitches, those amenities which are held by some to be indispensable to the playing of decent cricket are now on their way. In the past few years many hundreds of miles of new tarmac road have been laid, with a rising toll of fracture, laceration, and death. Electricity arrived some time ago in the overhead cables, and is altering the sleeping habits of the town. "Rediffusion" brings Mozart and the cricket scores into every backstreet, and some years ago water flowed into the town for the first time through pipes, bringing (for its first few months) such a wave of diarrhœa as the local wells had never been able to produce.

The Village Green is certainly changing with remarkable speed, and it is easy for the outsider to be misled by its rapidly changing new look. Rural society, however, is much the same the whole world over, conservative to a degree, and with a wealth of lore that runs strongly below the surface, no matter how the patterns on the surface change. And for all the water pipes, the pylons, and the new roads the Village Green still remains very much the Village Green.

The pitch here has a growing history, for it is something over 40 years since the first doctor and his wife arrived—in the days when the bicycle was still a curiosity, when they had to face many days of hard travel along narrow "bush paths", and when every device was used locally to discredit their work. With these two the game began, the doctor's readiness for each day's play being signified by the ringing of a bell which still stands on the present pitch. He and his wife are still vividly remembered by a few of the older inhabitants, through whom we, in our turn, are reminded of the days before cricket became established.

We are, therefore, perhaps more fortunate than some in being, through the continuity of our history, conscious of how close we are in time to the unregenerate days of Non-Cricket. And this is perhaps more important than it might appear, since attitudes are not to be changed in a matter of a generation, they must be taken into account in shaping tactics and strategy. The other important reason for mentioning history is that, since this particular club has always had to be more or less self-supporting, progress from the start has been by struggle and often by improvisation—i e , learning to make new uses for the resources at hand, and learning to do without what you cannot afford And this is, as I shall suggest later, an attitude which must guide the conduct of cricket in such places if it is to be played for a final win

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[1] *Lancet*, 1958, i, 951.

[2] Williams, C. D. *ibid* pp. 863, 919.

Since those days, however, the pitch has been twice moved, and greatly expanded and improved and now, perhaps, as a result of this growth and *prosperity faces* a new danger—the danger of trying to become an accurate small-scale replica of a county ground at home, using the same techniques and methods We are faced in fact with the danger of forgetting that the problems still differ as much from those in England as *they did in earlier days* And this danger faces neighbouring clubs as well

The Setting and its Problems

Some more interesting aspects of the game, however, must affect our attitude to medical education, and the way in which it is planned

What are We to Teach About ?

Leaving aside for the moment the revolution in social thinking which has to be undertaken by any doctor when he moves from a European background into the tropics, there is first the technical content of any curriculum In a setting in which the incidence of particular disease is topsy-turvy by comparison with what he has known in which the age-mortality curves are all awry in which preventable malnutrition is the scourge of childhood and in which the *natural history of any disease is very often* quite different to the same disease *in Europe, it is* plainly unsound to expect the curriculum of a Western medical school to be adequate for those who are going to spend their working days in the tropics.

There is little point in instilling the minutiæ of appendicitis, perforated duodenal ulcer, carcinoma of the rectum or lung, when these conditions are *rarely seen It is* misleading to teach that intussusception is an ileal disease affecting the infant and presenting with a certain symptom-complex, when in fact it is a cæcal disease affecting adults and presenting with quite a different picture It is dangerous to imply that the bottle is a possible substitute *for the breast when it is virtually out of the* reach of the vast majority of the population

It is equally misleading to teach that the diagnosis and management of chronic peptic ulcer depends in the first place on radiology, when it is commonly of a type very difficult to *display radiologically,* and the *opportune moment for* laparotomy has to be judged as much by social factors that are quite unknown to European medicine It is dangerous to paint rupture of the uterus as a rare condition best treated by hysterectomy, when it is a comparatively common one best treated by suture

Such examples could be multiplied indefinitely but the conclusion to be drawn is obvious It is not enough merely to add a course of " tropical medicine " on to the present form which medical training takes there must be some attempt instead to teach of " medicine in the tropics "

Tactics of Medical Practice

But such things are perhaps only the beginning of the doctor's metamorphosis , reorientations are needed towards the *practice of medicine which go* far beyond this, and which require the doctor to escape from the bonds of habits to which he became accustomed when he was a student

In the matter of techniques, *for* example

The *setting is one of rural life* the background one of often-superstitious custom The home teams evolved their rules for their own version of the game long before any European arrived and though many of their old techniques may be positively harmful, yet some are admirably adapted to the local resources, being as effective as our own new-fangled (and expensive) *methods* They are not to be automatically rejected (as *they* often are), and doctors must remind *themselves that there* can be no rule-of-thumb approach to the use of techniques

The carefully boiled leaf, so much affected in the dressings of sores, need not automatically be *replaced* by the imported and expensive bandage before progress is made and while it may be amply justified to insist on retaining in toto the sterile-cutting strokes of the surgically trained batsmen (with all the expensive *paraphernalia* which these presuppose), it *may be* equally wrong to *lift* a *premature* baby from the warmth of its mother's back and set *it in* an *incubator*

Again, the economic resources of most tropical countries are severely limited, and we offer nothing but a gratuitous and unnecessary discouragement to self-help if we misguidedly suggest that good medicine can only be practised where there are expensive facilities and techniques It may seem quite logical to us, for instance, to treat an œdematous *protein-deficient child* with a tin of skimmed milk, or ' Casilan ' but if we give the impression by so doing that these are the only weapons for the purpose, rather than preventing the condition with a diet of fish or beans (or whatever other protein happens to be local and cheap) we are in the long run doing more harm than good

Strategy

But important as reorientations of curriculum and tactics *may* be, even more important is our attitude to strategy For what we conceive to be the necessary long-term strategy determines not only what sort of student we *aim to get for medical* practice in the tropics but also how *we educate him—in the widest sense of that term*

In this country, against a backcloth of gradually developed social services we can set a highly developed preventive and public-health service Though it is obviously one of the keystones of our health programme, it is also the one which most of us forget about, or take for granted, most easily With these preventive services established, and in a country where *population density* is high and distances short, we can very satisfactorily divide clinicians into the general practitioners and the consultants, grouping around the latter a host of technical advisers and expensive facilities

There is one other very relevant factor on which we can also rely in this country And that is that every child, almost from the age of five upward, is tutored directly or indirectly in the sciences from which Medicine stems Even therefore if he never practises Medicine he understands its roots Things, of course, are very different in the tropics

In the tropics, however, there can seldom be such division of labour and each clinician must, ideally, have in himself therefore the elements of all—the attitudes if not the technical proficiency There is no comparable background *of preventive services or of child education* to fall back on, no such wealth of technical advice or expensive facilities, the distances are vast, the population density low, the setting rural, not urban or industrial In such a setting to model *medical* practice on the English pattern (with its sharp distinctions between those in hospital and those outside, between the specialist and the G P) is very bad strategy Rather must each doctor be conversant with the disciplines and attitudes of all the doctor-categories we know at home, and his strategy must be enlarged to include the strategy of them all—the educational, the preventive, and the social, as well as the more purely clinical skills he is taught in *his formal medical* course as a student

The Implications

From this background certain conclusions seem to follow I speak, of course, only for what I have seen in West Africa, and the conclusions may not be valid for other parts of the tropics—though I suspect that they are

Adaptation of Practice

What is urgently needed is a great deal of careful thought in adapting European medical practice to the local scene Tactically this involves the willingness to adapt methods of practice already learned to those which the country can afford and which are effective This in itself involves a good deal more imagination and understanding than many people are willing to admit And often there may be a good deal of very understandable local sensitivity on this point, especially when it comes to the training of students The feeling, that "to adapt methods of practice already learned to those which are effective and which the country can afford" may imply to some that a second best is being fobbed off on the local students Nothing of the sort is, of course, being attempted The techniques we learn, the methods we use, and the attitudes we try to inculcate in British teaching *may* be as unsuitable as overcoats to a tropical community And in our anxiety to establish our good faith we must be careful that we do not go to the opposite extreme of trying to transplant all the detailed paraphernalia of a British teaching hospital holus bolus into the tropics

Strategy

In a country where the main causes of illness and death are infective and nutritional, health education, preventive medicine, and a real understanding of the health problems of traditional rural life are at least as important as an efficient curative service But if these measures are to be effectively applied at all, they must depend for their prosecution on rural medical officers liberally equipped with the necessary imagination and energy They cannot depend on centralised administration for their expansion It is true, of course, that as independence grows, the strategy of medical services is controlled more and more by politics outside the doctors' control, but, nevertheless, the whole framework so imposed is moulded by those who work it

Training of Doctors

The inescapable conclusion, therefore, is that the training of doctors for such countries must be redesigned Simple arithmetic shows that an adequate supply of doctors to deal with the needs of tropical countries will depend for the foreseeable future on Western help in their training Thus, in West Africa, for instance, the only English-speaking university with a medical faculty is designed to take up to 50 students a year If all these students pass their examinations without fail, and if there is no "wastage", and if each of them were to practice for 30 years within Nigeria alone, the maximum force of doctors provided for is thus 1500

If the present population of Nigeria alone (estimated at about 30 million) were to remain static, and all doctors go into clinical rather than into administrative practice, this would therefore give a proportion of 1 doctor to every 20,000 of population—and this in a country where distances are vast compared with Great Britain

An adequate medical service, therefore, cannot for many years depend solely on African doctors trained in Africa, but will have to include both European doctors and African doctors trained in Europe With its wealth of means, too, Europe will necessarily dominate the postgraduate training scene. New thought must be given to these groups, and their training redesigned.

Firstly, in its technical content, to rebalance teaching with the countries' disease patterns in mind This is not just a matter of the altered incidence of disease, but, more important, of natural history Such conditions, for example, as pulmonary tuberculosis, toxæmia of pregnancy, intussusception, measles, and peptic ulcer are simply not the diseases that we know by those names Much of the pattern of disease is in fact still obscure and waits patient observation and systematic recording A pattern, however, of which enough is known to make a start on teaching students and postgraduates

Secondly (and much more important), the education of doctors must be redesigned to develop new attitudes not relevant to European medical practice Of course it is important that the tropical doctor should be taught something of tropical infections and their vectors, but there are essential reorientations that go far beyond this and the student must escape from the past obsession of Tropical Medicine with microscopes, which has dogged him for so long Instead, he must be given something of the economic, social, and cultural setting in which he is to practise Effective medical practice in the tropics depends largely on how far he is able to adjust himself to this new setting It is not for the many, but the few mental pliability, imagination (rather than erudition), a capacity for improvisation, and considerable gifts of "sympathy" (in its exact sense) are the qualities most needed

Some Suggestions

The upkeep of doctors is an expensive item in the economy of any country What can be done to make both the pre- and post-graduate training of doctors more relevant to their tropical practice ?

In most British universities only a tiny proportion of students come from, or go to, tropical countries and it is obviously not practicable to alter the content and method of teaching in an ordinary degree course for these few On the other hand, by conforming to the pattern designed for British students who will practise in Britain, their training as it is at present leaves overseas students frankly unprepared either in character or technique to deal with what will face them

For the Overseas Student

The problem can in part be solved by a year's internship in a tropical teaching hospital, during which the newly qualified houseman has time and opportunity to adjust himself to the altered surroundings of his practice The value of such a year will obviously depend both on the capabilities of the individual concerned and on the provisions made by the teaching staff for his encouragement and adaptation Here is a challenge as well as a great opportunity to the tropical universities If the internship period is merely conducted on lines familiar in Britain, it will fail If it sets out, instead, to provoke the imagination, and lays emphasis on the social setting and natural history of the country's disease, it may succeed

Even so, however, the tropical teaching hospitals cannot hope to have sufficient appointments for all the graduates available and by their very nature are not entirely the best place to teach the implications of rural health In order, therefore, to expand their capacity, and to achieve a valuable balance in their postgraduate teaching, such teaching hospitals might perhaps consider the setting up of an Institute of Medicine attached to the teaching hospital but with a number of surrounding affiliated rural hospitals and dispensaries (The valid prerequisites which such hospitals and dispensaries should possess in order to qualify for "recognition" as part of the teaching body would in themselves form an interesting contrast to those demanded in this country) Such an institute would aim to set before both local and expatriate doctors the readjustments which are required for fruitful practice, and give them some experience of rural medicine in the affiliated hospitals The rural hospital, as well as the student would gain greatly by such an arrangement

For Other Graduates

Even then, however, there will be many students from abroad who have to do their internships in Britain, and so will British students who later elect to go into the Colonial Service For these

(*a*) Some similar course of medicine in the tropics (rather than Tropical Medicine) might well be provided This perhaps ought to be frankly freed from the dictates of a diploma curriculum, and concentrate instead on the wider view of medical practice in tropical countries (Or it might include some such "second paper" as suggested in a *Lancet* annotation[1]) There is a growing body of clinicians experienced in tropical practice who might be drawn upon to help, during their periods of home leave in Britain, with such a course

(*b*) To extend the body of clinicians with insight into the conditions of tropical medical practice, exchange systems between the senior departmental staff of individual British universities and their tropical counterparts might most valuably be extended But such experience would only be of value if the period of secondment were sufficiently long, and if, by spending a major part of it in rural centres, there was opportunity for grasping the basic health problems of the country

The tropical teaching centres would not be the only ones to gain by such increased interchange of doctors

Specialist Training

By both British and tropical postgraduate schools it should be recognised that there are some specialties more urgently needed than others In countries in which the "infant" mortality is in the region of 300–400 per 1000 within the first 5 years of life, where malnutrition forms the backcloth against which most disease patterns in children are played out, where the patterns of "normal child" development are often yet uncharted, the pædiatrician stands easily at the top of specialist requirements And as Prof Richard Ellis has pointed out,[3] some postgraduate training in pædiatrics should be provided for every doctor who seriously intends to practise in the tropics

This again involves a shift in emphasis quite foreign to the traditions of practice in this country

Conclusion

Since World War II, many have become more conscious of the cultural and educational role which, by its unique nature, the Commonwealth is superbly placed to assume Within this role the adaptation and applying of our heritage of medicine is one of our obvious opportunities

In this age of mass-production and quick results we are perhaps more prone than ever to see the solution of health problems in the tropics in terms of mass programmes of immunisation, suppressives, injections, free milk, insecticidal spraying, and so forth Such things are invaluable, and it is not to decry them to say that they are inadequate to the whole task The basic problems of health are still largely social, to be solved at community, rather than at mass, levels, and to be solved by doctors whose training is not only sufficiently catholic for the task but is also designed to develop the highest levels of adaptability

As Dr Williams wisely remarks, "It is not the scientific knowledge that is lacking, it is the will to give ade[illegible]ing to the necessary medical personnel"

[illegible] R. W. H. Personal communication, 1953

In England Now

A Running Commentary by Peripatetic Correspondents

I MAY not look mechanically minded but at least I know how to work the tape-recorder That is more than Derek, my junior partner, can say, either on or off the record

I stayed behind on Friday afternoon to dictate half a dozen reports and letters into the thing, ready for Sylvia to type on Saturday morning It was a pleasant weekend down on the river, just the sort of weather to leave the junior partner and our secretary to hold the fort in town If I do not start taking it easy now all those years of grinding away will have been wasted For all I know a coronary may be just around the corner

I got back to town with a sunburnt neck and some nice trout in the back of the car The next move was to find someone to tell it to. The surgery was empty so was Sylvia's cubbyhole Just a note on my desk to say that Derek had rather a lot of visits to make, and Sylvia was off with a sore throat I looked around for the letters to sign they were usually put out on the blotter The appointments would have to go out by the midday post or be telephoned instead The river had washed all the details from my memory, so I turned to the tape-recorder and switched it on There were the nasal overtones I reluctantly accepted as mine, droning out the weary tale of Mrs Green's low backache and frigidity We had just recapped about her coccyx when there was a click The spools went round in silence for a long time Then more clicks and rattles A voice that was unmistakably Derek's asked what the hell it had done now A panic soprano shrieked that darling had washed out all the rest of the old buffer's letters by twiddling that switch There was another ten seconds' silence, and then a duet of giggles Just as this was getting rather boring, the baritone suddenly asked who was going to tell the boss on Monday morning I was intrigued to know the answer myself Sylvia was to have a sore throat, and Derek would stay out all day until the old boy had got the fishing stories off his chest

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SIR,—I am a French surgeon who makes his holiday in your so beautiful country and I borrow the pen of my landlady to write to you very quick because I see in your journal a letter which makes me very sad I think the three gentlemens which write this letter essay to kill in one foul swoop, as you say in your *language, so expressive, the sacred memory* of the illustrious Emile Coudé, of who I have the honour to be the grand nephew It is only last week ago when my assistant at the Salpêtrière say to me that there is a patient who cannot pass the water in the antechamber "The catheter" I cry. "Alas" responds he "I have already try" showing me the straight catheter of M Jaques "Imbecile! give me the catheter of my Uncle Coudé"—at last! the water she come and again a little more of glory is added to a name which the *Société* Internationale d'Urologie should revere but would make to fall into the mire "Over my dead corpse" I cry and sign myself

HERCULE COUDÉ

Coudé Rebent,
Blackpool sur-mer

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The stars of the *Michelin Guide* have long been reverenced by gastronomes, motor-car drivers, and compilers of guides, so that there is now scarcely a single travel brochure which does not ape their infallibility by classifying its wares in the asterisk fashion This valuable aid has now spread to surgery, and a recent volume offers a *Michelin Guide* to fractures I see endless possibilities in the system, and the fashion will probably spread I look forward to a new edition of *Tidy*, starred unduly

- * Diseases you should have—of benefit to the physician and not much trouble to the patient
- ** Diseases best avoided—curable but expensive
- *** Diseases you should not have—inexpensive but incurable
- **** Recherché and distingué diseases, appealing to physicians only
- ***** Fatal diseases

Students' Guide

1958 1959

Medical Schools

At Oxford University there is at present no "quota" for medical students, the preclinical entry is about 75 per year, of whom about 12 may be women. Some of the colleges have formed themselves into groups for the purpose of considering applicants to read medicine and the following two extracts from the *Gazette*[1] refer to this arrangement

> "University, Balliol, Trinity, St Johns and Jesus Colleges and St Peter's Hall will act as a group in considering candidates for admission to read medicine Candidates should apply in the normal way to the college of their first choice, but will subsequently be asked if they wish to be considered at the same time by the other colleges The examination for these candidates will be held on 23–25 March, 1959"
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> "Candidates for admission to any of the colleges Exeter, Oriel, Magdalen, Brasenose, Corpus Christi, Pembroke and Worcester Colleges should apply in the usual way, but will subsequently be asked if they wish to be considered also by the six other colleges named above If they do so wish, they will be allowed to place these in order of preference and their application will then be considered by each college in turn"

The entry to the clinical school is limited to 32 students a year, the majority coming from the preclinical departments of the university, but some coming from other universities These students may read for the degree of their own university, or if they have spent three years in an approved university, passed the equivalent of the Oxford 1st B M examination (organic chemistry, anatomy, physiology, and biochemistry), and taken an honours degree in the arts or sciences, for the Oxford B M degree

The new department for the Nuffield professor of surgery, Prof P R Allison, has been completed, and consists of twin theatres and laboratories, and two wards, all equipped to meet the professor's special requirements The new department for the Nuffield professor of clinical medicine, Prof L J Witts, is now almost completed Two new wards are in use and the research and teaching laboratories will be open shortly Plans have been prepared for new departments of anaesthetics biochemistry, and pathology, and a new outpatient block Even with the development of the new departments of teaching and research, together with the provision of an increased number of teaching beds, the university does not intend to increase the size of the clinical school Its aim will continue to be to provide the maximum amount of individual instruction and to give the student direct access to a large number of patients during his clinical training The tutorial system which has long been an integral part of the preclinical course at Oxford is continued throughout the clinical course This traditional tutorial system is one of the most valuable parts of the curriculum

At the University of Cambridge the number of candidates wishing to study medicine continues to exceed the number of places available and all college entries are subject to a university quota Two changes have been made in the regulations for the final M.B examination. The first relates to the period of clinical instruction in midwifery and gynæcology The regulations are amended so as to specify requirements of (*a*) six months' instead of three months' clinical training, (*b*) two months' instead of one month's residence in a maternity hospital, (*c*) instruction in antenatal and postnatal care Students who began their clinical training before Oct 1, 1956, however, will be allowed to proceed to the final M B examination on producing evidence satisfying the midwifery and gynæcology requirements previously in force The second change is designed to permit undergraduates who by the end of their second year's residence have obtained honours in the natural sciences tripos and have qualified in anatomy and physiology, and who wish to undertake a course of non-medical study during the third year in Cambridge, to take the final M B examination at the same time as their contemporaries who devote three years to the tripos and qualifying examinations The requirement that a candidate for either part of the final M B examination shall produce evidence of having completed five years of medical study has been amended to restrict the requirement to part II only of that examination The Cambridge medical student normally completes three of these five years as an undergraduate in residence and on Oct 1 following graduation begins clinical studies at a recognised hospital If, in the circumstances mentioned, the third year is devoted to non-medical study the student will begin hospital training with two years' medical study only to his credit, but will be allowed to count as part of his third year of medical study after graduation the period of three months during which he attends the long vacation course in elementary clinical methods He will then be able to take part I of the final M B (pathology and pharmacology) in the December of his third academical year at hospital and part II (medicine, surgery, and midwifery and gynæcology) in the following June, if he begins hospital training in the July immediately following his qualification for the B A degree either in his clinical school or by taking the long-vacation course in clinical methods in Cambridge

LONDON SCHOOLS

London University bears a different relation to its medical faculty from other universities, whereas they have one school of medicine each, London has twelve autonomous schools, each of which is closely linked with one of the teaching hospitals, as well as University, King's, and Queen Mary Colleges, all of which take medical students for some part of the preclinical course All the medical schools are now open to men and women students

At University College, which has the largest preclinical teaching and research staff in London, medical students taking the preclinical course come into close contact with students in other faculties, particularly with science students and research-workers who are specialising in anatomy, physiology, biochemistry, and pharmacology Every encouragement is given to students who pass the 2nd M B examination with credit to spend an extra year's study for the B SC (special) degree in anatomy or physiology Scholarships and exhibitions supplemented by the Ministry of Education are available for at least 12 students each year to take the B SC course This provides an admirable introduction to research methods and outlook, useful to the medical graduate in the clinical as well as the preclinical fields The first stage of the new biochemistry building in Gower Street came into use last autumn and the second stage will be ready later in the session The accommodation vacated by the biochemists will provide for the expansion of the physiology and pharmacology departments and the teaching and research resources of those departments will thereby be greatly strengthened Students accepted for the full medical course receive their clinical training at University College Hospital Medical School The dean of the faculty of medical sciences is Prof J Z Young

King's College provides courses for the 1st M B and 2nd M B examinations of the University of London for students who will be going on to King's College Hospital Medical School, St George's Hospital Medical School, or Westminster Medical School for their clinical studies No student may begin these preclinical courses who has not also been provisionally accepted by one of these hospitals for a clinical course King's College, with its faculties of arts, laws, natural science, engineering, and theology, provides the full activity of university life Applications for admission to the medical faculty in October, 1959, should be made at once, though applications may be considered up to the end of October, 1958 For admission in October, 1960, application between April and October, 1959, is advised

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[1] *Oxford University Gazette*, no 2071, June 13, 1958

The arrangements made by the joint committee of QUEEN MARY COLLEGE and the London Hospital Medical College ensure that the teaching in physics, chemistry, and biology fits in closely with preclinical teaching Most of the places are taken by London Hospital men and women, but applications from students with other hospitals in view are considered During the 1957–58 session 51 first-year medical students passed through the departments

At UNIVERSITY COLLEGE HOSPITAL Medical School there have been no major excitements during the academic year 1957–58 The annexe to the hostel has continued to show its worth and now 103 students are able to live on medical-school premises U C H together with its sector hospital at St Pancras now has a minimum of 1000 beds, and the nearby St Pancras Hospital is being used more and more for the clinical teaching of undergraduates The new Rowland Hall is much used for both clinical lectures and social activities The hard tennis courts at St Pancras are also proving popular with students and nurses The sports ground and its new pavilion at Hendon, which is within thirty-five minutes of U C H, is being used more and more and already ideas for increasing the size of the ground are being explored The rebuilding of the dental hospital and school has not yet begun, but there are indications that a start will be made before March, 1959 Linked with the rebuilding of the Dental Hospital and School and the consequent increase in the number of students, plans are well forward for a new student House to provide ample accommodation for social activities This will replace the existing Medical Society's rooms in the medical school

The Medical College of ST BARTHOLOMEW'S HOSPITAL is housed in new buildings ideally situated in Charterhouse Square where, in addition to the College hall of residence, there is a gymnasium and tennis and squash courts The basic science departments of zoology and comparative anatomy, physics, biochemistry, anatomy, physiology, and pharmacology provide tuition for premedical and preclinical students in modern laboratory accommodation In addition there are research facilities for all these departments About 30 to 35 are accepted every year from Oxford and Cambridge as clinical students There is a number of entrance scholarships in arts and in science, and internal scholarships are offered to a limited number of suitable candidates taking an honours B SC course in the year after passing the examination in anatomy and physiology During their final year students have the opportunity of spending a few days with a general practitioner, and an adviser in general practice is on the staff of the college to help with these matters

CHARING CROSS HOSPITAL Medical School has during the past year acquired additional accommodation on the corner of Bedford Street and the Strand This space is being used to provide a more spacious library and a larger and more airy common-room for women students, writing-rooms, and other student amenities, as well as larger offices for the accounts staff The space thus released in the main building is being adapted to provide better facilities for teaching and research, and in particular to house a newly instituted professorial unit in obstetrics and gynæcology In addition to this new chair, readerships have been established in pharmacology and anatomy In the final examinations for the M B, B S degree all those who presented themselves for the examination in pathology last autumn were successful, and there was a similar 100% pass-rate in medicine in the spring On that occasion the only two honours awarded for surgery in the entire University were won by Charing Cross students

At ST GEORGE'S HOSPITAL Medical School the work of modernisation is going ahead rapidly The greater part of the new laboratory space and the club rooms will be complete by the beginning of the new academic year All the usual activities of the school have been carried on successfully despite the rebuilding operations, and the school looks forward to a return to normal working in October University approval has been given to the establishment of a chair in medicine and it is hoped that a professor will take office in July, 1959

At GUY'S HOSPITAL Medical School the two and a half years of preclinical studies are designed to prepare the student for the clinical work which will follow, and particularly for the eventual practice of medicine There is a close link between the medical school departments and the wards Oxford and Cambridge students are admitted for the three clinical years The aim at Guy's has always been to encourage responsibility from the moment the student enters the wards A three-monthly series of dresserships and clerkships are arranged in the general wards and in special departments so that students accept supervised responsibility for patients, and the emphasis is on bedside and outpatient teaching rather than organised lectures There are, however, lectures and demonstrations organised by the directors of the departments of surgery, medicine, obstetrics, pædiatrics, and anæsthetics in order to cover the whole curriculum Preregistration appointments are available for those newly qualified, and every encouragement is given to men of promise to obtain the higher degrees and diplomas It is a condition of entry to the medical school that students should join the Clubs' Union which covers all athletic and intellectual activities and includes membership of the Students' Club

At KING'S COLLEGE HOSPITAL Medical School, stage II of the new extension will be ready for occupation at the beginning of the Autumn term Stage I, which was completed in November, 1957, provides on the top floor accommodation for the new medical unit under the direction of Dr Clifford Hoyle, on the middle floor a practical pathology laboratory with places for 60 students, and on the ground floor additional rooms for student amenities, including offices for the *King's College Hospital Gazette* and the Clubs and Societies Union Stage II will contain on the top floor an extension to the department of chemical pathology consisting mainly of research laboratories The middle floor, again consisting mainly of research laboratories, will provide accommodation for the new surgical unit under the direction of Mr Harold Edwards On the ground floor there will be a clinical lecture theatre with 32 tiered seats Adjacent is a demonstration room which will be used for clinicopathological demonstrations where all aspects of selected diseases will be displayed for varying periods A student-health consulting-room with dressing-rooms, rooms for medical and surgical tutors, and a council room are also provided on this floor The new building will be formally opened on Nov 4 by Queen Elizabeth the Queen Mother, Chancellor of the University of London

The school admits clinical students for the London, Oxford, and Cambridge degrees The dental school provides courses for the B D S and L D S diplomas, and each year 50 medical and 25 dental students are admitted Students for the London degrees do their preclinical training at King's College London, where they have the advantage of associating with students of all faculties King's College Hospital has 550 beds (including Belgrave Hospital for Children) It is situated in the heart of a large residential area and it has one of the busiest outpatient departments in London with an ample supply of clinical material King's College Hall is within five minutes' walk, and it is still fairly easy to find comfortable lodgings in the vicinity The school has the use and clinical control of 200 medical, surgical, and obstetric beds for undergraduate teaching at nearby Dulwich Hospital, where the instruction is undertaken by consultants from King's College Hospital and by some of the consultants of Dulwich Hospital who have been appointed associate teachers in the medical school The arrangements whereby students gain first-hand experience of general practice have been extended At their discretion individual students can now spend up to one week in residence with a general practitioner, the school bearing a part of the cost

During the past year the number of applications at THE LONDON HOSPITAL Medical College has remained high Application can be made at any time after reaching the age of sixteen, or passing the General Certificate of Education at ordinary level, whichever is the earlier Applicants are interviewed as soon as possible after they apply, and they are told of the result of the interview within a few days This policy is still proving of value, since applicants are not left in uncertainty about their chances of obtaining a place Applicants who are unable to obtain 1st M B exemption at school spend one year at Queen Mary College, but the number who need to do this steadily decreases For entry to Queen Mary College for 1st M B work, students must satisfy University entrance requirements, but application to go there should be made through the London Hospital Medical College In cases where the applicant from school is able to proceed to either Oxford or Cambridge, the place offered for the whole course becomes automatically transferred for clinical work at a later date The tutorial system in both the preclinical and clinical periods has been extended during the past year and continues to provide a useful method of linking the various parts of the curriculum The departments of physiology and anatomy now regularly run B SC (special) courses in physiology and anatomy, and scholarships are given as a result of the 2nd M B examination to enable suitable candidates to take part in these courses There is no doubt that these senior studies leading to the B SC degree are of great value to students in their future careers Research facilities continue to expand in both the preclinical and clinical field New laboratories for clinical research under the direction of the medical and surgical units have been opened and are proving of great value They have a close association with the professional departments of biochemistry and experimental biochemistry, ensuring that the highest standard of chemical advice will be available to workers in the clinical field Being in the centre of an industrial and residential area, the hospital continues to attract an unrivalled variety of clinical material to its busy outpatient departments Junior research fellowships have been established by the college, the tenure of which is normally one year, so that graduates who have done their house-appointments may gain experience in and have opportunities for original research under supervision. There has been no difficulty in all the newly qualified graduates getting a preregistration appointment, and the majority are able to hold at least their first appointment at the teaching hospital The athletic side of the college has been greatly helped by the opening of a new pavilion at the sports ground at Hale End

ST MARY'S HOSPITAL Medical School has received approval from the University of London for the first stage of the extension of its building and it is expected that this will begin in December, 1958 The extension has become possible as a result of the money raised by the centenary appeal of the school four years ago and also a generous gift by the Wellcome Trustees The university is providing the balance of the cost of the building which will greatly improve the teaching and research facilities of a number of the preclinical and clinical departments when it is completed in three years' time The number of applications for admission to the medical school continues greatly to exceed the number of places and much time is spent by the selection committees in interviewing candidates The Academic Board has decided to reduce the time spent on the introductory clinical course from ten to three weeks, beginning in October, 1958, and a committee is examining the curriculum with a view to other possible changes in the preclinical and clinical courses Princess Margaret honoured the Musical Society by attending a performance of *The Pirates of Penzance* on Dec 11, 1957

For some time the MIDDLESEX HOSPITAL Medical School has been planning the rebuilding of its premedical and preclinical departments A site was obtained very close to the present school and work was started at the end of December, 1957 The building is planned in three phases, the first containing lecture theatres and the large teaching laboratories, together with a special theatre capable of seating 350 and suitable either for lectures or for use by the Students' Dramatic and Musical Societies, &c This section should be completed in time to be used during the first winter term of the session 1959–60 It is hoped then to continue immediately with the second phase, comprising research laboratories, professorial and administrative rooms, dining hall, &c , and accommodation for the Student Health Service, which is run by one of the consultant staff Finally the third phase will be the residential college to accommodate 175 students This block will also include amenities for all students of the school, common-rooms, squash courts, music room, billiards room, games room, &c One of the most cogent reasons for this rebuilding scheme is the need for improved accommodation for students at all stages, and the building committee has given particular thought to the provision of facilities for student activities and to the encouragement of a corporate life within the school, essential in broadening both the general education and the special training of a doctor

The number of applications for admission remains very high, and the school asks prospective candidates to apply two years to eighteen months in advance of the proposed date of entry It is not essential to have any knowledge of chemistry, physics, or biology before entry, for the school teaches these subjects for the 1st M B and admits students to these classes who have satisfied the minimum entrance requirements of the University of London Direct entry to 2nd M B classes may be obtained by those who have gained exemption from the 1st M B through the necessary advanced-level subjects in the General Certificate of Education Students who have carried out their preclinical studies at Oxford or Cambridge are admitted for the clinical course There are excellent clinical facilities, augmented by an arrangement with the Central Middlesex Hospital which allows students to attend there for some instruction as clerks and dressers Certain house appointments are, of course, recognised for preregistration purposes and are reserved for students who qualify from the school. There are also many research appointments in the Bland-Sutton Institute of Pathology, the Courtauld Institute of Biochemistry, the Barnato-Joel Laboratories (Physics), and the Institute of Clinical Research The sports ground at Chislehurst, over twenty acres in extent, provides all the usual facilities and representatives of the various student clubs serve on the athletic-ground committee

During the year 54 students qualified from the ROYAL FREE HOSPITAL School of Medicine, of whom 2 gained honours Extracurricular student activities have included an ambitious but successful production by the Dramatic Society of Arthur Miller's play *The Crucible* This was taken to France in the Easter vacation, under the auspices of the Central Bureau for Educational Visits and Exchanges, and a performance was given for the staff and students of Lille University In athletics the school has provided 4 members of the University women's eight and the same 4 rowed in the British women's eight which competed in the European Championships A third-year student, who is captain of the University Women's Athletic Club and English women's cross-country champion, was second in the women's A A A mile this season The school has been well represented on the Committee of the University of London Students' Union, first by last year's vice-president and this year by the secretary A feature of the year has been the increasing interest shown by senior clinical students in the school's voluntary scheme of training in general practice Some 40 students have attended local practices either continuously for a fortnight, or once weekly for three months, and on present showing it seems that there will be even more attendances next year

ST THOMAS'S HOSPITAL Medical School admits students in October for the course leading to the London M.B , B.S degree They are accepted for premedical or preclinical entry and should apply as soon as they have taken their ordinary levels of the General Certificate of Education and not later than the end of July in the year preceding that of the proposed date of entry Students from the Universities of Oxford and Cambridge are accepted for their clinical training in April and October There are entrance scholarships for both preclinical and clinical students, all of which qualify for Ministry of Education supplementary awards For those London students who do well in the Second Examination for Medical Degrees, scholarships are available to help them to sit for an honours B SC degree in physiology or anatomy Students accepted for preclinical work who are subsequently successful in gaining entry to Oxford or Cambridge are given clinical vacancies There is a wide selection of prizes awarded every year, and after qualification many preregistration and research appointments are available Twice a year there is a very successful course for the final F R C S examination Great stress is paid during clinical training to ward and outpatient work, lectures being kept to a minimum The school has an excellent athletic ground at Cobham, Surrey, some forty-five minutes distant Squash is played in London and the boat club is a flourishing concern, sending a crew every year to Henley The school owns two sailing dinghies, one on the Welsh Harp and one at Burnham The past year has been a very successful one, for the school won the rugger, hockey, fencing, and rowing inter-hospital trophies In support of the Arts there are Choral, Photographic, and Art Societies, while instrumentalists can join the Hospital's Symphony Orchestra which rehearses at the school Every year there is a summer play and a Christmas revue, an event of some importance Films are shown by the Film Society, and the Medical and Physical Society, dating back to 1771, arranges clinical meetings and also invites men and women distinguished in fields outside medicine to lecture during the winter terms

The WEST LONDON HOSPITAL MEDICAL SCHOOL is recognised by the Universities of Oxford and Cambridge for the undergraduate clinical course, and it is hoped that the University of London will shortly restore the recognition which the school previously held In view of the proposed amalgamation of the hospital and school with Charing Cross no more new students will be accepted after October of this year, but there will still be some facilities for students revising for the qualifying examinations

At WESTMINSTER MEDICAL SCHOOL the number of clinical students remains constant at about 200 This is the optimum number, having regard to the clinical facilities available in the Westminster teaching group The applications for admission show a slight decline, but the standard of those accepted is at least as high as in the past The number of students who qualified with medical degrees in 1957 was a record for the school The Westminster teaching group comprises Westminster Hospital (430 beds) in which clinical practice in general medicine, surgery, and obstetrics is undertaken (the orthopædic, ophthalmic, and ear, nose and throat departments are also in the main hospital), the Gordon Hospital (100 surgical beds), The Westminster Children's Hospital (120 beds), and All Saints' Hospital (50 beds) for the practice of gynæcology and urology A close affiliation with St Stephen's Hospital provides very valuable additional clinical practice in medicine Instruction in practical midwifery is also given at St Stephen's Hospital, the Nelson Hospital, and St Teresa's Hospital, and in fevers at the Western Hospital, Fulham Under a voluntary scheme students may reside for a fortnight with general practitioners to see the work of their practice Special instruction in tuberculosis is provided by a fortnight's residence at the King Edward VII Sanatorium, Midhurst, and the teaching of mental diseases is carried out at the Netherne Hospital, London, S W 17 40 vacancies a year in the Westminster Hospital teaching group have been recommended for pre-registration posts, and competition for these is keen A new laboratory has been provided for the chemical pathology department A department of experimental surgery has been organised where already some notable research work has been carried out An additional medical firm will shortly be instituted at the Gordon Hospital The new sports ground at Cobham, Surrey, has been an unqualified success and the improved facilities have been reflected in a higher standard of play and a large number of successes in all outdoor sports

At the SCHOOL OF DENTAL SURGERY of the ROYAL DENTAL HOSPITAL of London, students who have completed the first medical or comparable examination devote one year to the study of general and special anatomy and physiology In the next three years of the course, after preliminary instruction, both theoretical and practical, in dental mechanics, dental materials, and the techniques required for dental conservation work, they attend lectures and clinics on general medicine and surgery at Charing Cross Hospital Medical School and lectures and practice in dental surgery at the dental school Degree students attend for a further period of four or six months before completing their final examination

OTHER ENGLISH SCHOOLS

In the UNIVERSITY OF DURHAM the extensions to the department of anatomy and to the animal house are nearing completion and they should be ready by the end of September As part of the general college plan to provide more residential facilities for students it is hoped to start work in 1959 on a new hall of residence for 225 male students, and conversion and additions to the present buildings should shortly provide accommodation for an additional 80 women students The college has also rented a large hostel from the Ministry of Pensions and National Insurance which, after renovations have been completed, should accommodate an additional 500 male students by next October The hostel will be known as the Eustace Percy Hall, after the late Rector of King's College Once again the Medical Students' Council has been active in representing the interests of medical students both in the college and on the British Medical Students Association Mr Peter G Wood has been elected president of the British Medical Students Association The Medical Athletic Union and the Medical Society have completed their customary full programme of sporting events, visits, lectures, and social activities

At the UNIVERSITY OF BIRMINGHAM* the number of applicants wishing to enter the medical school greatly exceeds the number of places available, and requests for admission should be made by April for first-year courses and by April of the preceding year for second-year courses Applicants within the United Kingdom are interviewed as soon as possible and told the result of the interview within a few days There are 14 places available annually for first-year courses (students from the Colonies or Dominions are generally required to enter upon first-year courses) and about 100 places per annum for men and women for second-year courses in medicine and about 45 per annum in the School of Dentistry It is hoped in the near future, with the building of a new dental hospital, that the annual entry to the School of Dentistry will be increased considerably At present preclinical instruction in dentistry is given in the medical school at Edgbaston and clinical teaching in the Dental Hospital in the city The library service in the medical school is excellent in that not only have students access to one of the largest collections of up-to-date medical literature in the provinces, but the resources of the whole University Library are open to them More especially the medical library has a comprehensive collection of textbooks available on fortnightly loan, and additional copies of textbooks are kept in a reference section for use in the library only A supplementary service is arranged with Messrs H K Lewis, enabling students to borrow standard books at a reduced subscription Since all medical books are housed in one department of the medical school, the student has the advantage of access to all monographs, general medical reference works, and bibliographical tools necessary for clinician and research-worker Ten scholarships are available for selected students to spend an extra year to take the B SC course in either the honour school of anatomical studies or of physiological studies

Students from Oxford, Cambridge, and other universities are encouraged to study clinical subjects at Birmingham. Two interesting scholarships provide the opportunity of spending three months in residence in either East or West Africa principally to gain experience in tropical medicine although part of the time might be spent in some other clinical department. Advanced clinical students may spend some time with selected general practitioners and a prize has recently been instituted for an essay on some topic of general practice. The entire curriculum is under review and an attempt is being made to integrate, as far as possible, the teaching provided by the several departments. The volume of preclinical and clinical research continues to expand. About 300 publications from the faculty of medicine are listed in the current Research Report of the University, and 21 higher degrees were awarded in medicine last year. The Annual Scientific Meeting of the British Medical Association was held in Birmingham in July, under the presidency of Prof. A. P. Thomson, dean of the faculty of medicine. Sport at Birmingham is organised by students through the Guild of Undergraduates, and students may join, without further subscription, any of thirty clubs. The Physical Education Department runs training and coaching schemes which cater for all standards. Sailing and rowing excepted, all sports can be played within 400 yards of the medical school. Future plans include a new physical education department, a sports centre, and a swimming pool.

At the UNIVERSITY OF LIVERPOOL* the outstanding event of the year was the official opening of the new medical school by Queen Elizabeth the Queen Mother on May 7.[1] The new building houses the research laboratories of the departments of medicine, obstetrics and gynæcology, pathology, bacteriology, pharmacology and general therapeutics, and radiodiagnosis, six tutorial classrooms, three lecture theatres, two large class laboratories, the dean's offices, a staff common-room, and a committee room. 91 new students were admitted to the M.B. course in October, 1957, 42 into the first year and 49 into the second year. The number of applications for admission is slightly down on previous years, but a full complement of students will begin their studies in October, 1958. There have been no changes in the requirements for exemption from the 1st M.B., and passes at the advanced level in chemistry, physics, and biology (or botany and zoology) are still required. Discussions are proceeding on the implications of the new recommendations of the G.M.C. on the medical curriculum, but no changes have as yet been made. A full-time readership in medicine has been established, and Dr. C. A. Clarke appointed to the post. Prof. T. N. A. Jeffcoate is visiting Canada, U.S.A., and the West Indies as Sims-Black Commonwealth Travelling Professor in obstetrics and gynæcology. Prof. R. M. Gordon, who has been a professor in the Liverpool School of Tropical Medicine since 1930, retires from the chair of entomology and parasitology at the end of the session after long and distinguished service. Mr. A. McKie Reid retires from the post of lecturer-in-charge of the department of ophthalmology. Dr. Robert Coope, Mr. Hugh Reid, and Mr. John McGibbon retired earlier in the session after long and invaluable service to the university and medical school.

At MANCHESTER UNIVERSITY* the major change during the past session has been the introduction of revised regulations for exemption from the 1st M.B. examination. As from October, 1958, candidates who have passed in chemistry, physics, and biology (or zoology) at the advanced level of the G.C.E. will be entitled to exemption. In future, therefore, the majority of students will enter upon the second year of the course, and be able to complete their qualification in five years. The scheme whereby senior students who wish to do so may spend two weeks with a local general practitioner has been very popular.

At the UNIVERSITY OF LEEDS* the new premises for the department of psychiatry were opened in January, 1958; they are in Hyde Terrace, near the department of biochemistry. Three large houses have been converted for the use of the department and provide administrative, library, research, and teaching accommodation, and also accommodation where patients can be seen. While it remains the long-term plan to provide this accommodation within the teaching hospital, in the meantime these new premises add greatly to the facilities available to the department. The building of the Martin Wing of the teaching hospital is well advanced and it is hoped that the full-time professional units of medicine and surgery will be able to move into their new quarters before the end of next session. No big changes in the curriculum have been made during the past year, nor are any likely in the immediate future, though consideration is being given to entry requirements and the content of the premedical part of the course. There has been only a small reduction in the number of applications for entry, which continue to exceed the number of places available.

In the UNIVERSITY OF SHEFFIELD,* although new university building has not so far greatly affected the medical school, a generous grant from the Rockefeller Trustees has furthered the activities of the department of microbiology. Assistance from the Sheffield Town Trustees has enabled the University to take a larger share in developing the department of psychiatry, and the building by the United Sheffield Hospitals of the new Whiteley Wood Clinic (an extension of the idea of a psychiatric wing within a general hospital) has also greatly assisted the department. The laying, by Queen Elizabeth the Queen Mother, of the foundation stone of a new outpatient department for the United Sheffield Hospitals indicates definite progress towards the ultimate provision of a complete new teaching hospital.

The discussions regarding the curriculum, mentioned in last year's report, are expected to lead next summer to considerable changes in the clinical part of the course. The arrangements for clerkships and dresserships will be modified, there will be changes in examinations and timetable, and two "elective periods" will be introduced. Partly in order to assist the students in the arrangement of their work during these periods, Dr. I. B. Sneddon, lecturer in dermatology, has been nominated as director of clinical studies. A pilot experiment relating to the development of a "tutorial" scheme already shows much promise of success.

Prof. R. P. Jepson has resigned from the chair of surgery on his translation to the University of Adelaide, Prof. William Hobson from the chair of social and industrial medicine to take up a W.H.O. appointment in Copenhagen, and Dr. John Pemberton from the same department on his appointment as professor of social medicine in Queen's University, Belfast. The future of the department of social and industrial medicine in Sheffield is being given careful consideration by the University.

In the UNIVERSITY OF BRISTOL the number of applications for the undergraduate courses in medicine and veterinary science has remained as high as for several years past, and those for the course in dental surgery have further increased. Major alterations are now taking place in the teaching hospital to improve the clinical facilities and accommodation for students. Some modifications in the medical curriculum have been introduced, mainly with the purpose of allowing a greater amount of voluntary attendance in lecture courses. The new medical school is in the planned stage and building is expected to begin in the autumn. Extensions to the dental school are anticipated in the near future, so that more students can be accepted in the clinical years. The teaching staff has been expanded and a new chair in dental medicine has been created The veterinary school has further improved its clinical facilities, the chief addition this year being a new operating-theatre

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[1] See *Lancet*, 1958, i, 1066.

* The entrance requirements for the Universities of Manchester, Liverpool, Leeds, Sheffield, and Birmingham are laid down in the pamphlet, *University Entrance Requirements 1951–1955*, copies of which may be obtained from the Secretary to the Joint Matriculation Board, 315, Oxford Road, Manchester, 13. Additional faculty requirements may, however, be imposed; details can be obtained from the dean of the faculty of medicine in each university.

WALES

The WELSH NATIONAL SCHOOL OF MEDICINE last year sustained a serious loss in the death of Lord Aberdare, its president for many years The Court of the University of Wales has elected as his successor Sir Clement Price Thomas, who is a past student of the School During the past year, the details of the schedules of accommodation for the new teaching centre in Cardiff have been agreed with the Welsh Board of Health It may be some time before building can start, but there is every hope that the architectural competition can soon be announced for a centre in which educational and hospital accommodation will be completely integrated In the meantime, the school is proceeding with the building of a dining hall and library, which will have the effect of improving amenities for students Additional houses have also been acquired so that hostel accommodation will be adequate for all those who desire it The authorities of the school are at the moment, like many others, engaged in carrying out a revision of the curriculum, but although it is not likely that this will be completed for some time, improvements are being made especially in the direction of correlating teaching in different departments The Student Health Service of the University of Wales, which is administered by the medical school, is extending its activities and it is hoped to provide more and better accommodation One of the postgraduate diplomas which attracts many students from overseas—namely, the tuberculous diseases diploma—will, in future, embrace chest diseases with an alteration in title to diploma in tuberculosis and chest diseases (D T C D) This is the first step in developments which are contemplated in the department of tuberculosis During the past year, a careful review of the preregistration appointments in the Welsh region has been made, and efforts are successfully being completed to ensure that the time spent in these appointments becomes a real extension of medical education The cooperation of the regional consultants with the teachers of the school is assured

SCOTLAND

At the UNIVERSITY OF ABERDEEN the curriculum for the degrees of M B, CH B extends over six academic years Courses in the premedical and preclinical subjects are given in departments located in Marischal College and in Old Aberdeen which provide instruction to science as well as to medical students Laboratory and lecture courses in the three clinical years are conducted in the University buildings on the Foresterhill site where the main hospitals are, and clinical instruction is given in all the hospitals in Aberdeen During the year a building to accommodate a special research department in clinical midwifery was completed and officially opened on April 22 It is staffed by the Medical Research Council and its honorary director is the professor of midwifery Plans have been prepared for a new medical physics building on the Foresterhill site, but it is unlikely that work will be started until early in 1959 During the year a new medical ordinance promoted by the four Scottish universities has been approved It permits certain candidates for admission to the medical faculty to sit the professional examination in physics, chemistry, and biology without attending University classes in these subjects Each university can make regulations for this purpose, but so far the University of Aberdeen has not done so They consider that the time has come to review as a whole the ordinances which govern medical education in the four Scottish universities These were made as long ago as 1911 and are so restrictive in character that they interfere seriously with the prevailing mood of medical educationists in seeking experiment It is proposed that a conference of the Scottish universities should be held early next term to consider the question of preparing new ordinances The number of students for admission continues to fall, but it is still above the number of places available An increasing number of applications are coming from overseas students in various parts of the Commonwealth

At the UNIVERSITY OF EDINBURGH, the past year has been one of continuing activity The number of applicants for admission in October, 1958, to the M B, CH B course remains high in relation to the number of places available Those applying for admission for the course beginning in October, 1959, should submit their applications to the dean of the faculty by Dec 31, 1958 A limited number of undergraduate bursaries and scholarships are available to students in the faculty of medicine for advanced courses of study—e g, an honours course of instruction for the B SC degree The University conducts postgraduate courses leading to the diplomas in medical radiodiagnosis (2 years), medical radiotherapy (2 years), psychiatry (6 months full-time), public health (9 months), and tropical medicine and hygiene (6 months) Graduate scholarships and fellowships are also offered, being open to graduates in the faculty of medicine of any university, to graduates in the faculties of arts or science of any university who hold an honours degree, and to licentiates in medicine The holders of such awards are required to undertake research work in a department within the faculty of medicine The Edinburgh Post-Graduate Board for Medicine (see p 472), which is an advisory council to the University, provides courses of instruction leading to the higher qualifications granted by the Royal Colleges of Edinburgh

At GLASGOW UNIVERSITY the number of applications for admission to the medical school is very similar to that for last year, but it is still in excess of the number of available places The number of applications for entry to the dental school, which had shown a sudden and welcome increase last year, has gone up still further this year The veterinary school has also had more applications

Plans are well advanced for the building which will house the new department of virology and also an extension to the genetics department It is hoped that the new building will be occupied in two years' time The dental school has acquired an extensive site adjacent to the Dental Hospital, which will provide additional accommodation mainly for postgraduate activities In the veterinary school the animal hospital and associated buildings for clinical instruction are now in full operation The farm, which was purchased three years ago, is being developed as a field station, offering facilities for instruction in animal husbandry and preventive medicine It is hoped that a start will be made this year on a new unit for experimental surgery, which will be housed adjacent to the veterinary Hospital The most important staff changes are the promotion of ordinances for the institution of chairs in orthopædics and in infectious diseases The junior teaching staff has been augmented by several additions to the lecturer grade

At the UNIVERSITY OF ST ANDREWS instruction in the subjects of the clinical years of study is given at Dundee, while the premedical and preclinical subjects may be studied either at St Andrews or at Dundee The course of study lasts six years The annual intake of students to the faculty of medicine is limited to between 70 and 80 to ensure that the hospital facilities available are sufficient to allow of adequate clinical instruction being given to each undergraduate The laboratory accommodation in both preclinical and clinical years has been recently extended and provides excellent facilities for students Both at St Andrews and Dundee there are residences which accommodate undergraduates from all faculties Medical students in their early years are encouraged to reside in these to make contact with undergraduates of other faculties

IRELAND

At the UNIVERSITY OF DUBLIN, there has been a considerable increase in applications for places in the medical school, but admission is restricted so that the number in the clinical years will be approximately 50 The clinical tutorial system, instituted two years ago, continues to work satisfactorily The period of residence in a maternity hospital has been increased, and new courses in pædiatrics will be given jointly by the National Children's Hospital and the pædiatric staff at the Rotunda The teaching of pathology in the hospitals has been further extended Reconstruction of laboratories is now approaching completion, and plans are in hand for new accommodation for the department of pharmacology

The SCHOOLS OF SURGERY, DUBLIN, including Carmichael and Ledwich Schools, are attached by charter to the Royal College of Surgeons in Ireland. The college admits to the preregistration classes approximately 100 students each year The normal method of entrance is by competition in the preliminary examination, but a limited number of places is given to those with exceptional qualifications and to certain students selected by the Colonial Office, to which all colonial students should apply, because, owing to limitation of numbers, they cannot be admitted to the entrance examination Nearly all students take the Irish Conjoint Board's examination but some take in addition the London examination. The Schools were inspected by delegates from London University four years ago and as a result were "recognised" for a further period of five years After an inspection in 1957 the Schools were formally recognised by the Commonwealth of Massachusetts Students are medically examined at the start of the preregistration year and again before the start of the clinical years Two doctors give free medical care to students and there are a men's warden and a lady dean of residence to help students in obtaining suitable accommodation and in other ways The playing fields of 16 acres and the pavilions are among the best in Dublin. Recently the laboratory space for chemistry and physics has been doubled, two rooms for advanced work have been added to the anatomy department together with a new lecture-room and much additional apparatus obtained for the pathology, physiology, and physics department. In addition a large room has been constructed for the Men's Union.

The ROYAL COLLEGE OF SURGEONS IN IRELAND is in the unique position of being by charter an undergraduate school of medicine undertaking the full training in the basic sciences and in the preclinical and clinical courses In the college buildings in Stephen's Green in the middle of the city are the laboratories for biology, physics, and chemistry, and for biochemistry, physiology, and pathology, as well as an unusually large anatomy department, five large lecture theatres for formal lectures, examination, administration, and reception rooms, the college library, a restaurant for the students, and the Union common-rooms for men and women. For midwifery and gynæcology any of the three well-known Dublin maternity hospitals are available to college students and for general hospital work any of the ten Dublin clinical hospitals and the usual specialist hospitals are available The Students' Union caters for about twelve other societies—scientific, musical, dramatic, rowing, football, boxing, &c—and most of these compete with visiting universities, Irish or otherwise Students are examined radiologically on entrance, tuberculin-tested, and, if they wish it, given B C G The radiological examination is repeated before commencing clinical work The great majority of students take the examinations of the Irish Conjoint Board and a few take the English Conjoint and the London University examinations

At QUEEN'S UNIVERSITY, BELFAST, the number of entries to the medical school each year is restricted to 108, of which up to 20 places are reserved for the school of dentistry Priority is given to applicants whose parents are normally resident in Northern Ireland, but a number of places are reserved for selected candidates from Great Britain and overseas Details of the entrance requirements may be obtained from the Secretary, Faculty of Medicine, 25, University Square, Belfast, or from the Clerk of Admissions, Queen's University, Belfast The Institute of Clinical Science, which was opened in May, 1954, provides exceptional facilities for the clinical teaching of undergraduates and of research for postgraduates A new department of anæsthetics was opened during this year It is hoped to fill lectureships in therapeutics, mental health, and dental pathology in the coming session

The NATIONAL UNIVERSITY OF IRELAND has colleges in Dublin, Cork, and Galway

The medical school of UNIVERSITY COLLEGE, DUBLIN, has for over sixty years been the largest in Ireland It was founded by Dr John Henry Newman and formally opened as the medical school of the Catholic University in 1855 From 1882 to 1909 it was separated from University College, with which it was fully reunited in 1909 In 1956–57 the school had 500 undergraduates in training for the degrees of M B, B CH, B A O, in the National University of Ireland Annual entry is restricted to 100 During the past year the school's relations with its affiliated hospitals, the Mater Misericordiæ, St. Vincent's, the National Maternity Hospital, and the Coombe Lying-in Hospital, have been put on a new basis There are now professorial units with professors and tutors in medicine and surgery appointed by the college in each of the two general hospitals, and the college also controls all appointments to their junior teaching staffs Similar arrangements exist with the two maternity hospitals New chairs in therapeutics, pharmacology, and medical microbiology have been established in the college The senior professors of medicine and surgery are completely whole-time A number of other Dublin hospitals are associated with the school and attended by small numbers of its students or available for special purposes The school controls appointments to the teaching staffs of two great pædiatric hospitals—Our Lady's Hospital for Sick Children, Crumlin, and St Joseph's Children's Hospital, Temple Street.

For some years past UNIVERSITY COLLEGE, CORK, has restricted its entry to 36 medical and 12 dental students, only 2 of whom may be from overseas Selection is made by the premedical or predental examinations, since it is felt that this gives a better index of the student's capability of profitable study under university conditions than does any other method The school has reverted to the six-term period of study in anatomy, physiology, and biochemistry in preparation for the 2nd M B The introductory clinical course has been abolished Instead, the department of physiology gives instruction in clinical physiology in hospital during the last term, there is an introductory course in pharmacology, and the student receives instruction in elementary pathology, a question bearing on this subject being included in the professional examination in anatomy The results of this approach to the problem of "integration" are being watched Apart from obstetrical and specialist units, there are over 500 acute beds available for clinical study, distributed between three general teaching hospitals The small annual intake was chosen to enable the optimum student/bed and student staff ratio to be achieved Increasing attention is being given to research, since it is realised that teaching, though a primary function of any medical school, is not enough for maintaining its morale Notable contributions have already been made by the departments of biochemistry, physiology, and anatomy The resources of the department of anatomy have lately been augmented by the completion of two research laboratories, the cost of which was generously contributed by the Wellcome Trust, and in this recognition of its industry, the medical school sees a happy augury of future expansion and development.

GALWAY Medical School was established in 1849, as the medical school of the Queen's University in Ireland The Queen's University was replaced by the Royal University of Ireland in 1882, and the Royal University was replaced by the National University of Ireland in 1909 Despite these changes, the work of the medical school was carried on without interruption, and the teaching staff and graduates of each university body were recognised by the succeeding university body

University College, Galway, is one of the three institutions which are federated into the National University of Ireland Galway, like Cork and Dublin, has its own charter, but is subject in matters of major policy to the Senate of the National University of Ireland The medical school is housed partly in the University College buildings and partly in the nearby Galway Regional Hospital—neighbouring buildings forming, in effect, one unit from the school's viewpoint The hospital (recently erected at a cost of over £1½ million) contains general surgical, general medical, obstetrical, fever, pædiatric, eye, and ear, nose, and throat units The members of the senior staff of the hospital are all clinical teachers of the college, the medical school has, under the Health Act of 1953, been allowed to have a 50% representation on the special selection boards of experts who select candidates for appointment to senior hospital posts Thus it can be said that the medical school exercises a measure of control over the appointments to the hospital medical staff, and accordingly of the clinical teaching of the hospital All the professors of the clinical subjects are members of the hospital staff

Degrees and Diplomas

EXAMINING BOARDS

English, Scottish, and Irish Conjoint Boards

THE Examining Board in England by the Royal College of Physicians of London and the Royal College of Surgeons of England examines candidates for the qualifying diplomas of L R C P, M R C S Candidates satisfying the board's regulations in regard to the preliminary examination in general education are eligible for admission to the premedical examination in chemistry, physics, and biology, and are required to complete the professional curriculum subsequently at a recognised medical *school* Copies of the regulations, with a calendar showing the dates of examinations, may be obtained, free of charge, from the secretary to the Examining Board in England, the Examination Hall, Queen Square, London, W C 1

The Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have an arrangement by which, after one series of examinations, held in Edinburgh or Glasgow, or both, the student may obtain the diplomas—designated by the letters L R C P E, L R C S E, L R F P S—of all three bodies Candidates may work for the examination of the Scottish Conjoint Board at any of the recognised medical schools of Great Britain and Ireland The course lasts six years and includes, in addition to the preliminary examination in the natural sciences—i e, chemistry, physics, and biology—three professional examinations the first in anatomy and embryology, physiology, biochemistry, and biophysics, the second in pathology and bacteriology and pharmacology, and the final in medicine, surgery, midwifery, forensic medicine, and public health Details may be had from the registrar, 18, Nicolson Street, Edinburgh

The Conjoint Board of the Royal College of Physicians of Ireland and the Royal College of Surgeons in Ireland examines candidates for the qualifying diplomas of the L R C P I and L M, L R C S I and L M After passing an approved examination in general education, candidates are required to do a one-year course in chemistry, physics, and biology, these subjects being treated with special reference to their applications in medicine After passing the preregistration examination in these subjects a five-term course of anatomy and physiology follows There is then a preclinical term with an introductory course at the hospital and this is followed by three years' clinical work There are three professional examinations Candidates are accepted from most of the recognised schools at home and abroad, but in practice 99% of the candidates are from the Schools of Surgery, which are controlled by the Royal College of Surgeons in Ireland The Irish Conjoint Board thus differs from the English and Scottish Boards in that it has a large teaching school under the control of one of its constituent colleges

Apothecaries' Licences

The Society of Apothecaries of London grants the L M S S A Lond to candidates who pass the primary examination (which is held quarterly) and the final examination Final examinations are held monthly, except in September The minimum period of study is normally five years The four parts of the final examination may be taken together or in any order Regulations and a schedule of the required courses of study may be obtained from the registrar, Apothecaries' Hall, Black Friars Lane, E C 4

The Apothecaries' Hall of Ireland is an examining and licensing body Candidates for examination must be registered *medical students* The diploma, L A H Dublin, confers on holders the right of registration in the Medical Registers of Ireland and Great Britain An examination in practical pharmacy is a compulsory part of the qualifying examination A course of lectures in the subject is given at the hall prior to each session of examinations The latter are held three times yearly—in March, June, and November Further information can be had from the registrar, 95, Merrion Square, Dublin

UNIVERSITY DEGREES

Bachelor of Medicine and Surgery

All the universities in the United Kingdom, except Nottingham, Reading, Southampton, Hull, Leicester, and Exeter, offer baccalaureate degrees in medicine and surgery, conferred on the results of examination

HIGHER QUALIFICATIONS

Those who have graduated in medicine and surgery are at liberty to seek higher qualifications if they wish

Doctor of Medicine and Master of Surgery

Graduates holding bachelor's degrees can take the degree of doctor of medicine or master of surgery All universities with medical faculties in Great Britain and Ireland confer such degrees Liverpool offers the orthopædic degree of M CH ORTH

Master of Midwifery

The Society of Apothecaries of London grants the *mastery* of midwifery (M M S A) upon examination in obstetrics, pædiatrics, and public health The examinations are held in May and November, and regulations may be obtained *from the* registrar, Apothecaries' Hall, Black Friars Lane, E C 4

MEMBERSHIP AND FELLOWSHIP

The Royal College of Physicians of London confers the membership (M R C P), which is obtained by examination Examinations are held four times in each year, and medical graduates and licentiates of the college over twenty-three years of age may sit for it Details can be obtained from the Secretary, Royal College of Physicians, Pall Mall East, London, S W 1 Fellows of the college are elected annually at a general meeting *of the college*

The Royal College of Surgeons of England grants a *fellowship* to those passing the primary and final F R C S examinations The primary examination is open to those who hold a qualification registrable in the British Medical Register and to graduates in medicine and surgery of universities and medical colleges recognised by the council Subjects of the primary examination are anatomy (including normal histology), applied physiology, and the principles of pathology The final examination can be taken in general surgery, ophthalmology, or otolaryngology To be admitted to the final examination in general surgery candidates must produce evidence of having been engaged in acquiring professional knowledge for not less than three years after taking a recognised medical qualification, and of having held the requisite resident surgical posts during a part of that time. Candidates for the final examination in ophthalmology or otolaryngology must have been qualified for three years and must have held general and specialist resident posts during an aggregate period of eighteen months. The primary examination is held in February, June, and October, and the final examination is held in May and November. The college also grants a fellowship in dental surgery. The primary examination is open to those with a dental qualification registrable in the British Dentists Register, and to graduates and diplomates in dental surgery of universities and licensing bodies recognised by the council. Subjects of the primary examination are applied anatomy, and applied physiology, and the principles of pathology, with special reference to the teeth and jaws, and of the final examination surgery, oral pathology, and bacteriology in dental surgery. The Faculty of Anaesthetists has been formed within the college, and the College grants a fellowship in the Faculty by examination. Subjects for the primary examination are anatomy, physiology, pathology, and pharmacology, and for the final, anæsthesia and analgesia, medicine and surgery, and the application of the basic sciences to anæsthetics. Copies of the regulations and full particulars may be obtained from the Examinations Secretary, Examination Hall, Queen Square, London, W.C.1.

Medical graduates who desire to specialise in obstetrics and gynæcology may apply for entry to the Membership examination of the Royal College of Obstetricians and Gynæcologists (M.R.C.O.G.). A minimum of three years' residence in hospital posts recognised for the examination is required before application is made. The Fellowship (F.R.C.O.G.) is granted to members who are judged by the council to have advanced the science and art of obstetrics and gynæcology.

Graduates may become members of the Royal College of Physicians of Edinburgh (M.R.C.P.E.) on passing an examination, particulars of which may be obtained from the secretary, 9, Queen Street, Edinburgh, 2. The fellows are selected from among members by the council of the college, and receive the designation F.R.C.P.E.

Fellowship of the Royal College of Surgeons of Edinburgh (F.R.C.S.E.) is granted to medical graduates who pass the required examinations. The examination is divided into two parts—the first on anatomy, physiology, pathology, and bacteriology, and the second on the principles and practice of surgery and on one of four special subjects to be chosen by the candidate. Particulars of the regulations may be obtained from the clerk of the college, Surgeons' Hall, 18, Nicolson Street, Edinburgh.

The Royal Faculty of Physicians and Surgeons of Glasgow grants, after examination, a fellowship *qua* physician and a fellowship *qua* surgeon registrable by the G.M.C. as an additional qualification (F.R.F.P.S.). Admission is by examination and subsequent election. Candidates for the fellowship in medicine must have been in possession of a recognised medical qualification for not less than two years, and must have been engaged during one of these years in full-time clinical work in a recognised hospital and have spent one other postgraduate year in approved medical work. The examination comprises a clinical examination in medicine, written and oral examinations in the principles of medicine and medical pathology, and written and oral examinations in the practice of medicine and therapeutics. Candidates for admission to the fellowship in surgery are required to possess a recognised medical qualification and to pass a primary and a final examination. The primary examination consists of written and oral examinations in anatomy and in physiology, pathology, and bacteriology. Candidates who have passed the primary fellowship examination of the Royal College of Surgeons of Edinburgh, the Royal College of Surgeons of England, the Royal College of Surgeons in Ireland, or the Royal Australasian College of Surgeons will be exempted from the primary examination for the fellowship of the faculty *qua* surgeon. For admission to the final examination candidates must have been in possession of a recognised medical qualification for not less than two years and produce evidence that they have been engaged, after qualifying, for one year in full-time clinical work in a hospital approved by the council and for a further year in the study of surgery. The final examination comprises a clinical examination in surgery, written and oral examinations in surgical anatomy and surgical pathology, and written and oral examinations in surgery. Alternatively, candidates may submit themselves for examination in one of the following subjects: obstetrics and gynæcology, ophthalmology, or otorhinolaryngology. Details may be had from the Registrar of the Royal Faculty of Physicians and Surgeons, 242, St. Vincent Street, Glasgow, C.2.

Membership of the Royal College of Physicians of Ireland (M.R.C.P.I.) is granted on the result of an examination, the details of which may be obtained from the registrar of the college, 6, Kildare Street, Dublin. Fellows are elected by ballot from among the members, and receive the designation F.R.C.P.I.

Graduates seeking the fellowship of the Royal College of Surgeons in Ireland (F.R.C.S.I.) must pass in two examinations, a primary in anatomy, physiology, and the principles of pathology, and a final in surgery, including some pathology. There are three examinations each year. Exemption from the primary is given to candidates who have passed this examination since 1951 at the Royal Colleges of London, Edinburgh, or Australasia, or at the Royal Faculty of Glasgow. A full-time four-month course in preparation for the primary examination begins on Oct. 1 and March 1 each year: the number of places is limited. Further particulars may be obtained from the registrar, the Royal College of Surgeons in Ireland, Dublin.

The Faculty of Radiologists offers a Fellowship (F.F.R.) to medical graduates of five years' standing who have spent at least one year in general clinical work at approved hospitals, hold a radiological diploma, and have practised radiology exclusively for at least two years after obtaining that diploma. Candidates are required to pass an examination in radiodiagnosis or radiotherapy, and in general medicine, general surgery, and pathology. Candidates who hold higher medical or surgical qualifications may be exempted from the examinations in general medicine, general surgery, or pathology. Full particulars may be obtained from the Warden, the Faculty of Radiologists, 45, Lincoln's Inn Fields, London, W.C.2.

SPECIAL DEGREES AND DIPLOMAS

The regulations for the following diplomas can be obtained by applying to the examining bodies concerned.

Anæsthetics

The English and Irish Conjoint Boards offer diplomas in anæsthetics (D.A.). The Faculty of Anaesthetists grants a fellowship (F.F.A.) on examination.

Bacteriology

Diplomas in bacteriology are granted by the Universities of London and Manchester and in bacteriology and microbiology by the University of Bristol.

Child Health

Diplomas in child health (D.C.H.) are granted by the National University of Ireland and the English and Irish Conjoint Boards.

Clinical Pathology

The University of London offers a diploma in clinical pathology (D.C.P.).

Industrial Medicine

The Royal Faculty of Physicians and Surgeons of Glasgow, the Society of Apothecaries of London, and the English Conjoint Board offer diplomas in industrial health (D.I.H.)

Laryngology and Otology

The English Conjoint Board offers a diploma (D L O) for those who have made a special study of the ear, nose, pharynx, and larynx The final examination for the F R C S and for the F.R F P S may be taken in otolaryngology

Microbiology

The University of Sheffield awards a diploma in this subject after a *full-time* course of study extending over one university session Entrants will normally be expected to be graduates of a university, but the senate may deem other qualifications as equivalent for this purpose

Obstetrics and Gynæcology

The Royal College of Obstetricians and Gynæcologists grants by examination a diploma (D OBST) to graduates with postgraduate hospital experience in general medicine or surgery and in obstetrics The University of Dublin also offers a diploma (D G O) The higher qualification granted by the Society of Apothecaries of London has already been mentioned The final examination for the F R F P S may be taken in obstetrics and gynæcology

Ophthalmology

The English and Irish Conjoint Boards issue a diploma in ophthalmology (D O and D O M S respectively) The final examination for the F R C S and for the F R F P S may be taken in ophthalmology

Orthopædics

The University of Liverpool offers the degree of M CH ORTH which is open to medical graduates of an approved university who hold the fellowship in surgery of one of the British colleges or of the American College of Surgeons

Parasitology and Entomology

The University of London awards a certificate and a diploma in applied parasitology and entomology

Pathology

The English Conjoint Board offers a diploma in pathology (D PATH)

Physical Medicine

The English Conjoint Board offers a diploma in physical medicine (D PHYS MED)

Psychological Medicine

The Universities of London, Dublin, Durham, Edinburgh, Ireland (National University), Leeds, and Manchester, and the English and Irish Conjoint Boards offer diplomas in psychological medicine

Public Health

A diploma in public health (D P H) is granted by the English Conjoint Board and by all the universities of Great Britain, except Cambridge, Oxford, Birmingham, Reading, Sheffield, Nottingham, Southampton, Hull and Exeter, and also by the National University of Ireland

Radiology

The Faculty of Radiology grants a fellowship (F F R) The University of Edinburgh and the English Conjoint Board offer two diplomas—one in medical radiodiagnosis (D.M R D) and one in medical radiotherapy (D M R.T) The University of Liverpool offers a diploma D M R (D) or (T) obtainable by examination after a two-year course in diagnosis or therapy, after a further two years diplomates may be awarded the M RAD by presentation of a thesis

Tropical Medicine

A diploma in tropical medicine and hygiene (D T M & H) is granted by the University of Edinburgh, by the University of Liverpool jointly with the Liverpool School of Tropical Medicine, and by the English Conjoint Board The University of London has an academic postgraduate certificate and an academic postgraduate diploma in tropical medicine and hygiene

Tuberculosis and Chest Diseases

A diploma in tuberculosis and chest diseases (D T C.D) is granted by the University of Wales

DENTAL DEGREES AND DIPLOMAS

There are schools of dentistry at the Universities of London, Belfast, Birmingham, Bristol, Dublin, Durham, Edinburgh, Glasgow, Leeds, Liverpool, Manchester, Sheffield, and St Andrews (at Queen's College, Dundee), and at the University Colleges of Dublin *and Cork* in the National University of Ireland London University offers a B D S and an M D S, it also prepares students for the L.D.S of the Royal College of Surgeons of England This college has a fellowship in dental surgery (F D S) and a diploma in orthodontics (DIP ORTH) A fellowship is also granted by the Royal College of Surgeons of Edinburgh Edinburgh University offers a B.D S and an M D S, Leeds *grants* an L D S, a *baccalaureate degree* (B CH D), and mastership (M CH D), and Manchester *grants* an L D S, a B.D S, an M D S, and also a doctorate in dental science (D D S) Glasgow University and the University *Colleges of Dublin and Cork* grant a B.D S and an M.D S; and Trinity College, Dublin, offers a B DENT.SC. and an M DENT SC St Andrews no longer offers a diploma, but in its place a baccalaureate (B D S), and it has also instituted a doctorate of dental science (D D SC) It continues to offer a diploma in public dentistry (D P D) and an M D S All the other universities mentioned offer L D S, B D S, and M D S Licences in dentistry are granted by the Royal College of Surgeons of Edinburgh, the Royal Faculty of Physicians and Surgeons of Glasgow, and the Royal College of Surgeons in Ireland The Royal Faculty of Physicians and Surgeons confers a higher diploma in dental surgery (H D D) and a diploma in dental orthopædics (D D O)

Postgraduate Education

EACH university in the United Kingdom with a medical school is responsible for the postgraduate education of the region in which it is situated Each has a postgraduate education committee with a dean or director of postgraduate studies as its executive officer

IN LONDON

The British Postgraduate Medical Federation (University of London) provides postgraduate education in the medical and dental specialties, supplementing the opportunities available at the undergraduate schools and teaching hospitals and those provided by the three Royal Colleges The services of the staff of the central office of the Federation are available to all postgraduates, including those from the Commonwealth, the Colonial territories, and foreign countries, in advising on programmes of study and in making the arrangements necessary Each of the three Royal Colleges arranges lectures in various aspects of its specialty, and advises graduates on the suitability of hospital appointments and programmes of study for its higher qualification

British Postgraduate Medical Federation

The British Postgraduate Medical Federation, which is a school of the University of London, comprises the Postgraduate Medical School of London at Hammersmith Hospital (with its university departments of general medicine, general surgery, and pathology) and 14 Institutes, each associated with a special postgraduate teaching hospital or Royal College The numbers of students that can be admitted to the clinical practice of the hospitals with which the Institutes are associated are limited, resident clinical appointments are available to suitable students of the Institutes, and provide the most valuable form of postgraduate education There are opportunities for research by selected graduates At all the Institutes instruction is given throughout the academic year, it is suitable for graduates in the early stages of their specialist education and also for those who have completed their practical training Two or more years of hospital work in general medicine and general surgery after graduation are normally advisable before commencing work in the special branches The work at the Institutes is of an advanced type and is sufficiently comprehensive to enable graduates with suitable practical experience to prepare for higher degrees and diplomas Emphasis is placed on clinical and laboratory teaching, supplemented by lectures and demonstrations Each Institute has a reference library, and takes the current journals relevant to its specialty Most Institutes arrange short symposia, varying from one or two days to a week for Consultants, and there are one-day clinical conferences open to Senior Registrars, chiefly those in general medicine and surgery, throughout the country The programme arranged for the year 1958–59 will be found in the advertisement columns of this issue Short courses and other forms of continuing education for general medical and dental practitioners and local-authority medical officers are arranged at hospitals throughout the four Metropolitan regions, with the assistance of the Regional Advisers in postgraduate medical and dental education The Federation has arranged a ninth series of advanced lectures, entitled The Scientific Basis of Medicine, to be delivered two afternoons a week, at 5 30 P M , at the London School of Hygiene and Tropical Medicine, during the autumn and winter terms of the 1958–59 session The lectures are designed especially for research-workers and specialists in training and are open to all registered medical practitioners without fee Further details are given in the advertisement columns of this issue Three lectures on the Scientific Basis of Dentistry will be given early in 1959

It is essential for prospective postgraduate students from abroad to make their arrangements well in advance, and those who desire the assistance of the central office of the Federation are advised to get in touch with the Director of the Federation, Prof Sir Francis Fraser, M D , F R C P , at the central office, 18, Guilford Street, London, W C 1, as far in advance of their arrival in this country as possible Those sponsored by their universities, governments, or other official bodies receive first consideration in the allotment of vacancies Established specialists from overseas, here for a short time, who wish to see something of the practice of this country, are always welcome, they are regarded as visiting colleagues, and the experts in their specialties are always ready to receive them and let them accompany them in their work and teaching An information bureau of postgraduate activities in London and other university centres is maintained at the central office

The Federation awards annually a number of travelling fellowships, for the purpose of studying abroad, to graduates working in medical or dental schools or teaching hospitals of the University of London

The **Postgraduate Medical School of London** is associated with the Hammersmith Hospital It has university departments in medicine, surgery, and pathology The teaching in the clinical departments is based on ward work which is supplemented by lectures during three ten-week terms starting in January, April, and October A course for the university diploma in clinical pathology, lasting one year, is available for a limited number of selected students The department of radiology of the hospital provides courses for the diplomas in medical radiology of the Conjoint Board A year's course in anaesthesia, consisting of lectures and clinical training, is also provided All these courses begin in October Facilities for research are available for selected students

Address Ducane Road, London, W 12

The **Institute of Basic Medical Sciences** comprises the departments of anatomy, physiology, and pathology of the Royal College of Surgeons of England The Institute cooperates with other specialist institutes of the Federation in providing facilities for practical work and instruction in the basic medical sciences There are opportunities for research for selected graduates Full-time and part-time courses of 14 weeks' duration suitable for candidates for higher degrees and diplomas, begin in January and September A two-month revision course for primary F D S candidates is held twice a year beginning in December and June

Address Royal College of Surgeons of England, Lincoln's Inn Fields, London, W C 2

The **Institute of Cancer Research Royal Cancer Hospital** comprises the Chester Beatty Research Institute and parts of the departments of physics and radiotherapy at the Royal Marsden Hospital The Institute is concerned with all aspects of research into the causation and treatment of cancer, with the training of research-workers in this field, and with advanced teaching in biophysics, radiotherapy, and problems of atomic energy There are laboratories for chemical, biochemical, and histological investigations into cancer and allied diseases Facilities are afforded to those wishing to pursue research in the clinical and pathological aspects of cancer or the physical and biological foundations of medical radiology, and who may be working for higher degrees, such as the PH D The department of radiotherapy gives a lecture and demonstration course of one week's duration in May and November annually primarily for doctors from overseas, and accepts candidates to train for the diploma in medical radiotherapy A course of lectures for students studying for the M SC degree in biophysics commences in October

Address Fulham Road, London, S W 3

The **Institute of Cardiology** is associated with the National Heart Hospital Six appointments in senior-registrar and registrar grades are available in the hospital and the Institute to provide specialised training for postgraduates who have already had a sound grounding in general medicine Full-time and part-time courses of instruction of about eleven weeks' duration are held twice annually, starting in April and October, and two or three short intensive courses of lectures and demonstrations are held each year in February, June, and November, one of these is for general practitioners

Address 35, Wimpole Street, London, W 1

The **Institute of Child Health** is associated with The Hospital for Sick Children and the Postgraduate Medical School at Hammersmith Hospital, the Queen Elizabeth Hospital for Children, Hackney, also participates in the clinical teaching of the Institute The Province of Natal Model Welfare Centre offers facilities for the study and care of the healthy child The Institute provides tuition throughout the year in three terms of three months each, and in addition a series of lectures by specialists in various spheres is given each term Clinical clerkships are available for selected students

Address The Hospital for Sick Children, Great Ormond Street, London, W C 1

The **Institute of Dental Surgery** is associated with the Eastman Dental Hospital The object of the Institute is to provide postgraduate training in the special branches of preventive and therapeutic dentistry by means of clinical experience, lectures, demonstrations, and research Courses of various lengths are held from time to time in children's dentistry, orthodontics, conservative dentistry, periodontology, prosthetic dentistry, oral surgery, and oral pathology For candidates preparing for the F D S of the Royal College of Surgeons, courses lasting eight months are held twice yearly commencing in October and April For selected students junior staff appointments are available for this period In April and October there are revision courses, lasting eight weeks, suitable for candidates for the final F D S examination A course in orthodontics, of a year's duration, commences in October

Address Eastman Dental Hospital, Gray's Inn Road, London, W C 1

The **Institute of Dermatology** is associated with St John's Hospital for Diseases of the Skin Throughout the year clinical teaching takes place daily in the outpatient department and twice weekly at the inpatient department at Homerton Tutorials in clinical dermatology and histopathology of the skin are given twice weekly during term time In each of the university terms there is a series of lectures and weekly clinical demonstrations Special short courses in histopathology and in medical mycology are also held There are facilities for study and tuition in pathology, including mycology, radiotherapy, and physiotherapy Advanced students may also be eligible for clinical and research assistantships, the former of which are competitive A discussion of cases of special interest, to which students attending the courses are invited, takes place once a week

Address St John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London, W C 2

The Institute of Diseases of the Chest is associated with the Hospitals for Diseases of the Chest (the Brompton and London Chest Hospitals) On the medical side, a comprehensive full-time course is conducted for a limited number of graduates who are specialising in chest diseases, during the two terms beginning in October and January, and a more selective one during the summer term A larger number can be accepted for part-time study, which is suitable for those reading for higher medical diplomas Clinical instruction in thoracic surgery, including cardiac surgery, is given throughout the year, and there are courses in the October and January terms *Part-time instruction in radiology of the chest is given for* trainee radiologists Clinical demonstrations and lectures open to the medical profession are given each week

Address Brompton Hospital, London, S W 3

The Institute of Laryngology and Otology is associated with the Royal National Throat, Nose and Ear Hospital There is daily clinical teaching throughout the year The whole-time courses held twice yearly include basic sciences, three months, intensive lecture course, six weeks, practical revision course, two weeks, advanced revision course, two weeks Short courses on special aspects (such as endoscopy, audiology, pathology, aural surgery, and malignant conditions) *are given from time to time*

Address 330/332, Gray's Inn Road, London, W C 1

The Institute of Neurology is associated with the National Hospital and the Maida Vale Hospital for Nervous Diseases, which jointly form a teaching hospital The teaching is mainly by attendance on the hospital practice, supplemented by lectures and demonstrations Two courses in clinical neurology are held annually commencing in January and October Clinical instruction in neurosurgery is given throughout the year *Courses of clinical demonstrations (two weekly)* are held several times a year A course in the technique and clinical application of electroencephalography is held jointly with the Institute of Psychiatry twice a year Advanced students are appointed as clinical clerks in the wards or attached to the special departments and research laboratories

Address National Hospital for Nervous Diseases, Queen Square, London, W C 1

The Institute of Obstetrics and Gynæcology is associated with Queen Charlotte's Maternity Hospital, the Chelsea Hospital for Women, and the Department of Obstetrics and Gynæcology at Hammersmith Hospital The teaching is based on ward work and is supplemented by lectures and demonstrations during two terms of thirteen weeks' duration, which commence in March and September Short intensive courses of a fortnight's duration, held in June and December each year, are suitable for students preparing for the higher qualifications A week's course for general practitioners is held twice a year

Address Chelsea Hospital for Women, Dovehouse Street, London, S W 3

The Institute of Ophthalmology is associated with the Moorfields Eye Hospital In addition to teaching by means of attendance on the hospital practice, a routine lecture and tutorial course, normally covering two terms of approximately sixteen weeks each, is held twice a year commencing in March and October, the first part of the course is devoted to anatomy, embryology, histology, physiology, optics and elementary clinical instruction, and the second part comprises bacteriology, pathology, operative surgery, medical ophthalmology, and all aspects of ophthalmic disease Introductory courses, lasting one week, in orthoptics and contact-lens practice are held during each term Clinical teaching and lectures are given at a higher level for advanced students There are facilities for research for suitably qualified candidates

Address Judd Street, London, W C 1

The Institute of Orthopædics is associated with th Royal National Orthopædic Hospital Training in orthopædic to selected graduates who have already been trained in genera surgery and the basic sciences is afforded by means of clinica appointments, with opportunities for research For graduate requiring a less extensive period of education in the specialty and especially for those who have acquired practical experienc overseas or elsewhere, advanced courses are held at variou times during the year These are of seven to ten days' duratio Twice a year, in the spring and the autumn, a short revisio course of a week's duration in advanced clinical orthopædic is held Both the central hospital in Great Portland Street an the country hospital at Stanmore are attended by postgradua students

Address Royal National Orthopædic Hospital, 234, Great Portlan Street, London, W 1

The Institute of Psychiatry is associated with th *Bethlem Royal Hospital and the Maudsley Hospital* Trainin normally covers three years, after experience elsewhere i general medicine, and is based on responsible hospital dutie under supervision Regular series of lectures and demonstra tions are given throughout each of the university terms, clinical training continues throughout the year and include seminars and case-discussions Students who, because o previous experience, do not wish to take the comprehensiv course are able to attend limited series of lectures and clinical instruction For those who wish to specialise in child psychi atry a six-month course is held twice yearly A course in th technique and clinical application of electroencephalography is held jointly with the Institute of Neurology twice a year A year's course in abnormal psychology for the university postgraduate diploma in psychology is available to holders o an honours degree in psychology There are facilities for original investigations under supervision in the clinical departments and in the psychological, neuropathological, neuroendocrinological, electrophysiological, and biochemical departments

Address Maudsley Hospital, Denmark Hill, London, S E 5

The Institute of Urology is associated with St Peter's, *St Paul's, and St Philip's Hospitals* Comprehensive instruction is given in the wards, outpatient departments, operating theatres, laboratories, &c , throughout the year Weekend courses of demonstrations and lectures are held from time to time for higher examination candidates In addition lectures on venereology are arranged occasionally in cooperation with the Medical Society for the Study of Venereal Diseases, and arrangements can be made for graduates to attend a venereal diseases clinic In the winter months a series of lecture-discussions on urological subjects of interest to the whole profession are held on Wednesdays at 5 P M Limited numbers of clinical assistants are appointed to individual surgeons for personal tuition, and there are also research assistantships

Address 10, Henrietta Street, London, W C 2

ROYAL COLLEGES, HOSPITALS, SCHOOLS, &c

The Royal College of Surgeons of England has arranged a number of lectures and demonstrations to be held at the college A full-time clinical surgery course will be held in September and October, 1958, and in February and March, 1959 This will be limited to two groups of students, 15 in each In addition two series of 24 surgery lectures will be given during October and April and at the same time clinical conferences will be arranged at selected hospitals In anæsthesia three series, each of 36 lectures, demonstrations, and discussion groups, will be given in the autumn, spring, and summer Lectures and clinical demonstrations in oral, dental, and general surgery will be held in conjunction with the

Institute of Dental Surgery in May and October. Lectures and courses are arranged during the year jointly with the Institutes of Laryngology and Otology, Urology, and Ophthalmology. Specialists are available for consultation on postgraduate training in general surgery, dental surgery, plastic surgery, and anæsthetics. Facilities are now available for advice on postgraduate orthopædic training through the postgraduate orthopædic committee which has its headquarters at the college. Residential accommodation is available in the Nuffield College of Surgical Sciences. The Institute of Basic Medical Sciences, formed jointly by the college and the British Postgraduate Medical Federation, has arranged a programme of postgraduate teaching in the basic medical sciences (see above). Information on all these courses may be had from Mr. W. F. Davis, Deputy Secretary, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

The ROYAL COLLEGE OF SURGEONS IN IRELAND gives a four-month course in anatomy in preparation for the primary fellowship examinations. There are two courses in each year, one starting in October for the February examination and the other in March for the July examination, but students may join the course at any time. This is a fully comprehensive course. In addition there is a similar course starting at the same time in physiology and the principles of pathology. Details may be had from the registrar of the college.

At ST. MARK'S HOSPITAL, City-road, London, E.C.1, surgeons wishing to specialise in proctology may attend courses of one to six months, and postgraduate students working for higher degrees may come for one to four weeks' whole-time study.

THE LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE offers a number of courses. The following last for one academic year of nine months. The course for the University of London's academic postgraduate diploma in *public health*, commencing each year at about the beginning of October, is designed primarily for qualified medical practitioners who intend to engage in any branch of preventive medicine. There are now no vacancies on the course beginning Sept. 30, 1958. Students may elect to make a special study of one of the following: (1) child health, (2) medical statistics and epidemiology, (3) mental health, (4) occupational health, (5) tropical hygiene, (6) nutrition. Occupational health as a special subject, plus practical work and attendance at clinics (arranged by the school), is recognised by the Conjoint Board and the Society of Apothecaries as fulfilling in part the requirements for entry to examination for the diploma in *industrial health*. The course for the University of London's academic postgraduate diploma in *bacteriology*, commencing about the beginning of October each year, is intended to give advanced instruction to graduates in medicine, science (including veterinary science), or pharmacy who intend to follow a career in bacteriology. There are now no vacancies on the 1958–59 course. Applications for the subsequent session must be received not later than March 1, 1959. The number of places is strictly limited. The course of study for the University of London's academic postgraduate certificate and diploma in *tropical medicine and hygiene*, commencing about the beginning of October each year, is designed to give advanced training in tropical medicine. The preliminary C.T.M. & H. course occupies approximately the first 4½ months of the complete course. The final course consists of advanced study in one of two fields—clinical tropical medicine or tropical hygiene. The course for the University of London's academic postgraduate certificate and diploma in *applied parasitology and entomology*, commencing about the beginning of October each year, is open to candidates with acceptable qualifications in medicine, veterinary medicine, veterinary science, and science. The preliminary C.A.P. & E. course occupies approximately the first 4½ months of the complete course, which is planned mainly for people wishing to take up research or laboratory appointments abroad. There are now no vacancies on the 1958–59 course. Applications for the subsequent session must be received not later than April 1, 1959. The number of places is strictly limited. The five-month course for the Conjoint Board's diploma in *tropical medicine and hygiene* is held twice a year. The next courses begin on Oct. 6, 1958, and Feb. 23, 1959. A course in *statistical methods* applied to medicine and epidemiology is held annually on two days a week from about the beginning of January to about the end of April. Students without a medical qualification can be accepted. A ten-week course in *environmental control* is held twice a year, commencing next on Sept. 30, 1958, and Feb. 23, 1959. Although intended primarily for health inspectors from abroad, the course is so planned as to be of value to medical officers and others interested in the health aspects of environmental control both at home and abroad.

The ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE conducts courses of instruction (starting annually in March and September) covering the syllabuses for the examinations of the Conjoint Board for the diplomas in public health and in industrial health. The next courses will start on Sept. 12, 1958. Students are prepared too for the diploma in industrial health of the Society of Apothecaries. All tuition may be whole-time or part-time. Part-time courses may be commenced at any time. Lectures are given by the internal teaching staff of the institute and by external lecturers. For the diploma in public health, attendance at the health department of a local authority and fever hospital is arranged, and there are visits to places of importance to the public health. For the industrial-health course, practical sessions are arranged at appropriate clinics and departments of hospitals, and arrangements are made with various medical officers and others in representative industries for visits to works under their supervision. Full information, entry forms, and prospectuses may be obtained from the Dean, 23, Queen Square, London, W.C.1, or from the Secretary, 28, Portland Place, London, W.1.

The Institute is a medical corporation, incorporated by Royal Charter. Under its present name, the Institute came into being in October, 1937, as a result of the amalgamation of the Institute of Hygiene and the Royal Institute of Public Health, upon the granting of a supplemental Royal Charter to the Institute of Hygiene. Among its main objects and work are:

Laboratory work.—The bacteriological, chemical, and serological laboratories are available for the examination and investigation of pathological specimens, water, milk, sewage, &c.

The Museum of Hygiene.—The Institute maintains a permanent educational health exhibition, open free to the public daily from 9.30 A.M. to 5 P.M. at 28, Portland Place, W.1.

Lectures by medical and scientific authorities upon topics relating to public health and hygiene are given at spring and autumn sessions. The Harben and the Bengué Memorial Award lectures are delivered annually at the Institute, and the Blackham lecture triennially.

Examinations for the certificate and the diploma of the Institute are held twice yearly (in January and June) in London and at centres throughout the British Isles in the following separate subjects: general hygiene, school hygiene, and mothercraft and child welfare.

The TAVISTOCK CLINIC is an outpatient centre devoted to psychotherapy both of adults and of children on broadly psycho-analytic lines, and to providing training in certain skills in this field. Special attention is at present being given to the development of techniques in handling parents of disturbed children, to marital problems, and to group therapy of adults. In addition, the clinic and the associated Tavistock Institute of Human Relations are engaged in research in the fields of child development, personality, preventive psychiatry, and applied social science. A number of registrar and senior registrar posts are established in the adult and the children's and parents' departments. The following courses of training are available:

(1) Full-time training in psychotherapy, with special reference to the needs of the National Health Service, carried out in conjunction with the tenure of registrar and senior-registrar appointments in the adult department. Personal analysis is available as part of this training.

(2) A two-year full-time course in child psychiatry (for registrars)

(3) A two-year part-time introductory course in psychotherapy, including group experience (open to selected trainee psychiatrists from other N H S institutions)

(4) Introductory courses for general practitioners dealing with the patient-doctor relationship and with psychological factors in ill health

(5) A more advanced two-year course in psychotherapy in general practice for limited numbers of family doctors

(6) Several courses in the Rorschach method of personality assessment (by arrangement with the Institute of Human Relations), open to doctors with relevant experience

In addition there are training courses in clinical psychology, educational psychology, advanced social casework, and child psychotherapy, open to graduate psychologists (non-medical) and social workers, in some instances during their tenure of trainee posts or fellowships Both sides of the clinic also conduct regular case-conferences and other types of instruction with their internal students which may be open to limited numbers of suitably qualified professional workers from home or overseas on request and by permission From time to time lectures are advertised open to limited numbers of psychiatrists and workers in related fields Further information may be had from the Medical Director, 2, Beaumont Street, London, W 1

The TAVISTOCK INSTITUTE OF HUMAN RELATIONS is concerned with applied social research and the provision of advisory services in problems which may cover the family, the factory, the hospital, or the community Further information may be obtained from the Secretary, Tavistock Institute of Human Relations, 2, Beaumont Street, London, W 1

The INSTITUTE OF PSYCHO-ANALYSIS, 63, New Cavendish Street, London, W 1, provides training in psycho-analytic theory and technique The course is part-time and lasts about four years It includes a personal analysis, attendance at lectures and seminars (held in the evenings), and clinical work done under supervision Students are required to obtain general psychiatric experience at other clinics and hospitals since the Institute does not set out to teach psychiatry Completion of the course to the satisfaction of the training committee qualifies the student for independent work as a psycho-analyst On the recommendation of the training committee, the student is elected an associate member of the British Psycho-Analytical Society and the Institute of Psycho-Analysis Training in child analysis is available for senior students

The FELLOWSHIP OF POSTGRADUATE MEDICINE was founded in 1918 The Fellowship, whose offices are at 60, Portland Place, London, W 1, provides a bureau of general information on postgraduate work, and also arranges various courses of instruction to suit the special needs of postgraduates whose requirements are not met by other existing programmes The Fellowship's arrangements include

(1) Weekend courses, occupying the whole of a Saturday and Sunday These are given in various hospitals in such subjects as infectious diseases, general medicine, the rheumatic diseases, orthopædics, plastic surgery, and clinical surgery

(2) Courses specially suitable for, though not restricted to, candidates for the D C H, D OBST, M R C P, and F R C S (final) These include general medicine, general surgery, midwifery, and children's diseases Some are full-time courses, lasting one or two weeks, others are spread over longer periods, taking place in the mornings, afternoons, or late afternoons, they are intended particularly for postgraduates not free for full-time study

The *Postgraduate Medical Journal*, the official organ of the Fellowship, is published monthly and contains a special section devoted to general postgraduate news and information about the work carried on in all the main centres of teaching throughout the British Isles The Journal can be obtained by subscription or in single copies

The TUBERCULOSIS EDUCATIONAL INSTITUTE is a body composed of representatives from the Joint Tuberculosis Council and the National Association for the Prevention of Tuberculosis The Institute organises lecture and demonstration courses at home and overseas for doctors, and at home university centres for doctors, nurses, health visitors, social workers, and administrators Intensive three-day clinical courses for doctors are held throughout the year at King George V Hospital for Diseases of the Chest, Godalming, and East Fortune Hospital, Drem, East Lothian Short weekend lecture courses are arranged locally for general practitioners Particulars of courses may be obtained from the Secretary, Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W C 1

PROVINCES

Birmingham

The Board of Graduate Studies of the University of Birmingham provides a large number of extended and short intensive courses of instruction to help general medical and dental practitioners to keep abreast of recent advances Most of these are held at hospitals in Birmingham, but some are arranged at other centres, such as Coventry They endeavour to cover the needs of doctors and dentists practising in the West Midlands, but practitioners from further afield, particularly Birmingham graduates, are welcomed if they care to attend General medicine, general surgery, pædiatrics, obstetrics, neurology, neurosurgery, psychiatry, dental prosthetics, and general dental surgery are the main subjects covered In arranging these facilities the Board of Graduate Studies works in close cooperation with the Midland Faculty of the College of General Practitioners and the Central Counties Dental Postgraduate Committee

The Institute of Accident Surgery, which is affiliated to the Board of Graduate Studies of the university, holds short intensive courses in traumatic surgery at the Birmingham Accident Hospital Some are planned to help surgical consultants and trainees, some are for industrial medical officers and nurses, and others are for general practitioners Each year a five-day course in industrial ophthalmology is held at the Birmingham and Midland Eye Hospital

The University of Birmingham does not grant any medical diplomas and its doctorates of medicine and philosophy and its mastership of surgery are only given for theses providing a substantial advance in knowledge Graduates of universities other than Birmingham must have pursued original work in the Birmingham Medical School or in its teaching or affiliated hospitals for a minimum period of two years before submitting such theses The only courses of instruction for higher diplomas are for the diploma in psychological medicine of the Conjoint Boards (parts I and II in alternate years) and the M R C P (every one or two years) Facilities for parts I and II of the D M R D and D M R T are, however, available to those holding trainee appointments in the teaching hospital Attachments as observers and research-workers in the medical school and teaching hospital are arranged for large numbers of postgradaute students from other centres in England and from abroad, but no financial support can be offered and the expenses of all such attachments have to be met by outside sponsoring bodies or by the student himself The Board of Graduate Studies, in conjunction with the University Department of Social Medicine, pursues a number of research projects in which the help of general practitioners is invoked The chairman of the Board of Graduate Studies is Dr A G W Whitfield, The Medical School, Birmingham, 15

Bristol

The degrees of doctor of medicine (M D), master of surgery (CH M), and doctor of philosophy (PH D) are open to graduates of other universities, but to only those candidates who have pursued original research in the university for not less than two years In effect, this regulation means that these higher degrees are open to only those graduates of other universities who hold appointments on the staff of the university or of one of the Bristol hospitals The university diploma in psychological medicine is in abeyance The university offers a diploma in public health, and a course will be held in the session 1958-59 A few postgraduates are accepted for training for the D M R D and D M R T (Conjoint) and arrangements can sometimes be made for suitable candidates to hold a part-time post in the Bristol hospitals while doing the course. A course in child health lasting three months usually begins in October of each year, but in 1958 the course will not be held. Refresher courses for general practitioners consist of Sunday morning lecture-demonstrations in Bristol and occasional intensive weekend courses at hospitals in various parts of the South-West region. A Board of Dental Studies has been established to organise and direct dental studies in the university. A postgraduate course in medical physics for science students has been instituted. A review of preregistration appointments has been undertaken to ensure that only house-officer posts which have the facilities necessary for sound postgraduate training are recognised for the purpose. A medical postgraduate dean has been appointed.

Cambridge

The School of Postgraduate Teaching and Clinical Research includes the departments of experimental medicine, human ecology, medicine, and radiotherapeutics. In the John Bonnett Clinical Laboratories, pathological and biochemical services of the United Cambridge Hospitals are provided by university teaching officers under the direction of the professors of pathology and biochemistry. Particulars of the research activities of the school are given in the departmental annual reports, which are published in the Cambridge University *Reporter* in February each year. Prof. J. S. Mitchell took up office as regius professor of physic in July, 1957, and among the proposals submitted to the University in association with his appointment were plans for the development of the facilities of the Postgraduate Medical School and the United Cambridge Hospitals, in collaboration with the East Anglian Regional Hospital Board. An important step in this direction was the appointment of Dr. Leslie Cole as dean of the Postgraduate Medical School in December, 1957. The attention of the Council of the Senate and the Hospital Authorities has been drawn to the urgent need for the provision on a site close to the radiotherapeutic centre of Addenbrooke's Hospital of a building to house an Institute of Postgraduate Medical Studies, with lecture rooms, laboratories, and study rooms, and to provide more permanent accommodation for the departments of medicine and radiotherapeutics, both of which are at present in temporary buildings.

Between October and July in each academic year special sessions are devoted to teaching by members of the consultant staff of the United Cambridge Hospitals. Other teaching activities include clinical or clinicopathological meetings held on the second Friday of each month during term which give an opportunity for general practitioners and others to meet the staffs of the teaching hospital and of the various departments of the medical school. One-day symposia on subjects of particular interest to general practitioners are held monthly on Saturdays throughout the academic year. These symposia usually take the form of lecture-discussions followed by case-demonstrations. To meet the needs of practitioners who are unable to leave their practices on Saturdays it is proposed to hold one or two Sunday meetings during the coming year. During the summer of 1959 it is planned to arrange a longer course for general practitioners, from July 6 to 11 at Addenbrooke's Hospital. Accommodation and board will be provided in Downing College. Residential courses in midwifery are available for undergraduate and postgraduate students at the Maternity Hospital. All postgraduate courses and symposia are open without fee, subject to the terms of the Ministry of Health scheme, to practitioners who are under contract with an executive council of the National Health Service, and who have not less than 500 (or in the case of a rural practice 250) persons on their N.H.S. lists. Practitioners who do not qualify for a grant under the Ministry of Health scheme may be charged fees at rates corresponding to those which otherwise would have been payable by the Ministry. A course on Progress in the Biological Sciences in Relation to Dermatology has been arranged from Sept. 22–27, 1958. The course will consist of a number of half-day sessions each devoted to a group of papers on the same or related subjects. The course is designed primarily for those engaged in the clinical practice of dermatology but is open to any medically qualified person interested in the subjects under discussion. Courses are also contemplated on anæsthesia, diabetes, psychiatry, metabolic aspects of disease, and dental surgery. Further details of postgraduate facilities may be obtained from the Secretary of the Medical School, Tennis Court Road, Cambridge.

Durham

The part-time course for the diploma in public health ended in June. Seven of the eight candidates obtained their diplomas. The next course will begin in January and extend over five academic terms until June, 1960. Refresher courses for general practitioners were held during the year. These consisted of intensive weekend courses in medicine, pædiatrics, psychiatry, and obstetrics, and extended courses consisting of several afternoon sessions in various subjects. A number of local practitioners attended two-week resident courses in obstetrics in the Princess Mary Maternity Hospital. Postgraduate instruction in anatomy, physiology, pathology and bacteriology, and other subjects is always available by arrangement with the professors of the departments concerned. Several postgraduate students from overseas have been provided with suitable courses and research facilities leading to higher degrees.

Leeds

The University of Leeds grants two postgraduate diplomas, the diploma in public health and the diploma in psychological medicine. Both are now part-time courses, that for the diploma in public health being five terms. The course for the diploma in psychological medicine covers eight academic terms. Extended refresher courses for general practitioners, comprising one half-day session a week for six weeks, and weekend refresher courses on special topics are arranged from time to time both in the teaching hospitals and in regional hospitals. The secretary of the postgraduate committee is Dr. T. A. Divine, School of Medicine, Thoresby Place, Leeds, 2.

Liverpool

Postgraduate courses have continued as in previous years. Out of a total of 716 students in the medical school, 205 are postgraduates, 16 attended the course in general surgery, 19 in orthopædic surgery, 15 in public health, 11 in anæsthesia, 12 in psychological medicine, 25 in radiodiagnosis, 7 in radiotherapy, 4 in venereology, 67 in tropical medicine and hygiene and 22 the part-time M.R.C.P. course recently established. The course in general surgery is suitable for candidates who have already passed the primary examination for the F.R.C.S., but candidates for the course in orthopædic surgery must already hold the F.R.C.S., to become eligible to take the examination for the M.CH.ORTH. degree. The courses leading to the D.M.R.D. and D.M.R.T. extend over two years, candidates are usually found registrar appointments during the second year. In the course in anæsthesia, students are found appointments in recognised general hospitals to gain practical experience. Further information regarding university postgraduate courses may be obtained from the dean of the faculty of medicine.

The Liverpool School of Tropical Medicine offers a course of instruction for the diploma in tropical medicine and hygiene granted by the University of Liverpool. Two such courses are held each year, starting in the middle of September and the beginning of January and continuing for approximately three months. Only those students who hold a medical qualification registrable in the United Kingdom or otherwise recognised by the University, and who have attended the approved course of instruction in this school, are eligible to sit for this diploma. The school also provides courses in parasitology and entomology for students taking the diploma in public health granted by the University of Liverpool. Courses of instruction in veterinary parasitology and entomology are given during each academic session to Liverpool University undergraduates taking the M.R.C.V.S. diploma and B.V.SC. degree.

Manchester

Courses in preparation for the diplomas in psychological medicine, public health, radiodiagnosis and radiotherapy have been held during the past session and will be offered in 1958–59 A one-year course in medical statistics is available, but the course for the diploma in bacteriology will not be conducted during the session 1958–59 Refresher courses in industrial health have been held, and a series of lecture-demonstrations for general practitioners, given in conjunction with the College of General Practitioners, was very successful A similar series will be held on alternate Sunday mornings during the Michaelmas Term, 1958 The Dean of Post-Graduate Medical Studies is Mr R L Newell, F R C S , who is available for consultation by appointment

Oxford

The university committee responsible for postgraduate medical studies was recently reconstituted and its duties made the subject of a new university statute The first duties of this committee are to meet the obligations imposed upon the university by Act of Parliament—namely, keeping general practitioners informed of the latest developments in professional knowledge, and approving hospitals and posts therein for preregistration purposes Facilities for postgraduate medical studies are available in the Nuffield professorial departments of the university under the professors of medicine, surgery, obstetrics and gynæcology, anæsthetics, and orthopædic surgery Certain clinical appointments on the staff of these departments are open to specialist trainees from the Commonwealth In addition to the provision made in these departments for the training of specialists, there are approximately 20 trainee appointments in the teaching hospitals (the United Oxford Hospitals) and 11 in certain departments of selected non-teaching hospitals of the Oxford region These appointments (senior registrars) are in the following branches of medicine general medicine, pædiatrics, psychological medicine, chest diseases, pathology, general surgery, orthopædics and accident services, otolaryngology, ophthalmology, obstetrics and gynæcology, neurosurgery, plastic surgery, dental surgery, and radiology 6 of these are " paired " posts, the holders of which spend part of their period of training in a teaching hospital and part in a non-teaching hospital by mutual agreement Facilities for the continuing education of general practitioners are provided in hospitals at Oxford, Reading, Aylesbury, Stoke Mandeville, and Northampton Most departments of the United Oxford Hospitals may be visited by general practitioners on certain days throughout the clinical year (September to July) Practitioners may follow either an intensive course of a week or a fortnight (when programmes are arranged to suit individual requirements) or an extended course spread over a number of weeks or months In addition special short courses can be arranged for general practitioners All inquiries should be made to the Director of Postgraduate Medical Studies, Osler House, 43, Woodstock Road, Oxford, from whom further details of long and short courses may be obtained

Sheffield

The recently resuscitated D P H course was successfully concluded this session, but for various reasons another course is not to begin at once The development of the department of psychiatry has enabled the department to become increasingly a focus for regional postgraduate education in this specialty Other postgraduate activities include an experiment in which the usual intensive refresher course for general practitioners is being held in the hospitals of the Nottingham area instead of in Sheffield as in past years

WALES

Cardiff

Regular courses are conducted for the D P H (Wales), commencing in October every other year, and for the diploma in tuberculosis and chest diseases (D T C D) (Wales) (January to June each year) A special short course in tuberculosis is also held each year Prospectuses are available for these courses During terms, departmental provision is made for postgraduate teaching A standing arrangement also exists between the medical school (through its professorial departments), the teaching hospitals, and the regional board for regional consultants to spend short periods in Cardiff Special courses for general practitioners are arranged in association with the Welsh Board of Health—two short courses of 5 sessions each on selected subjects extending over one week in the autumn, and a fortnight's general course in the spring In addition, four weekend postgraduate courses in dentistry are being held for dental practitioners, and in these the regional hospitals most willingly cooperate Further information may be obtained from the Dean of Clinical and Postgraduate Studies, Medical School Office, 34, Newport Road, Cardiff

SCOTLAND

Aberdeen

Fortnightly refresher courses are held each year, mainly for general practitioners, which cover recent advances in medicine, surgery, obstetrics, pædiatrics, and other specialties From time to time extended courses of eight or ten weekly afternoon meetings are held There is also occasionally a Sunday-morning course for general practitioners when they can attend two lectures each Sunday for seven weeks, on subjects in medicine, surgery, pædiatrics, and midwifery The main postgraduate training is that given to registrars in all the departments of medicine In these posts registrars are rotated round the different wards and hospitals in their own specialty, and also they may spend periods in related departments A surgical registrar, for example, may go round the general surgical wards of the region but may also receive training in thoracic surgery, neurosurgery, orthopædics, pædiatric surgery, and otolaryngology In the same way a medical registrar may act for a time in a similar position in the children's and fever hospitals

Edinburgh

Postgraduate teaching in Edinburgh is arranged by the University in collaboration with the Royal College of Physicians and the Royal College of Surgeons of Edinburgh The courses are administered by the Edinburgh Post-Graduate Board for Medicine and cover the subjects of internal medicine, surgery, and basic medical sciences, in addition to refresher courses for general and dental practitioners Two courses in internal medicine, lasting twelve weeks, start in April and October each year These courses comprise lectures, lecture-demonstrations, clinical teaching, and clinical-pathological demonstrations, they are suitable for graduates wishing to specialise in medicine or who require a refresher course in the current outlook on internal medicine Two courses in surgery are held each year, starting in March and October These courses last twelve weeks and provide coordinated instruction in general surgery and in the specialist branches of surgery Clinical teaching in the wards of the Edinburgh Royal Infirmary and other general and specialist surgical units in the city has been arranged Graduates are thus able to spend a period in each unit, following the work of the department and obtaining systematic instruction A comprehensive course in the medical sciences of anatomy, physiology, pathology, bacteriology, and biochemistry is held in the summer, three hundred hours of instruction are given in this course, over a hundred of which are devoted to practical teaching, including work in an anatomy department This course is suitable for those requiring a final preparation in these subjects It is desirable that those taking this course should already have considerable basic knowledge Similar basic-science courses of ten weeks' duration, starting in October and March, are organised by the Royal College of Surgeons under the ægis of the Post-Graduate Board From July to September a course in clinical medicine is arranged in which clinical instruction in small groups is given in the teaching medical units in Edinburgh For those already holding higher qualifications short intensive courses in special subjects are held from time to time The numbers on these courses are limited so that discussion can be free Through the Director of Post-Graduate Studies, postgraduate students may be attached for clinical duties to the medical and surgical units in Edinburgh Preference is given to those who have attended the courses

The fourteen-day general-practitioner course, held in May each year, provides teaching either at the bedside or by means of lecture-demonstrations Emphasis is laid on recent advances in treatment, and free discussion, as well as constructive criticism by members of the course, is encouraged Instruction for local general and dental practitioners is arranged throughout the autumn term In addition, courses of one day's duration, on selected subjects, are held at intervals throughout the year Courses are often booked up several months in advance, so those intending to apply should do so early Applicants should write, giving particulars of their medical qualifications and postgraduate experience, to the Director of Post-Graduate Studies, Surgeons' Hall, Edinburgh, 8

Glasgow

Glasgow University Post-Graduate Medical Education Committee, representing the University and the Royal Faculty of Physicians and Surgeons of Glasgow, is offering the following courses during the coming session A nine weeks' part-time course in anatomy, physiology, biochemistry, pathology, and bacteriology will be held, as in previous years, from October to December The course is suitable for candidates preparing for the primary examinations for the surgical fellowships, and will provide a total of approximately 180 hours of instruction The course is organised primarily for the junior staff of hospitals in the Western Region of Scotland, but it is also open to other applicants A modified form of the course is available for trainees in anaesthetics reading for the primary examination of the F F A Clinical attachments to teaching units of one to three months' duration can be arranged in general medicine, general surgery, and various specialties for those proceeding to higher qualifications An annual course for the diploma in public health is available and a course for the diploma in industrial health will be arranged in any year in which there are sufficient applicants Short courses in other specialties are arranged when the demand arises and are advertised in the medical journals For the ensuing session a three weeks' course in mental deficiency and two weekend courses in chemotherapy have already been arranged The department of psychological medicine will hold a part-time course, extending from January to June, 1959, for candidates reading for the D P M Training in radiodiagnosis and radiotherapy, recognised for the D M R D and D M R T is available At least two refresher courses for general practitioners are held each year A very successful addition to the range of postgraduate courses has been the institution of short intensive courses on the use of radioactive isotopes These courses are organised by the staff of the regional physics department, which advises and assists hospitals on matters concerned with isotopes and electronic apparatus

St Andrews

Under the postgraduate training programme in the university a new combined clinical and medical sciences course will be held in Queen's College, Dundee, from October, 1958, to March, 1959 Those who have been accepted for this course will have a clinical attachment in a special subject of their choice and a supervisor who will guide their reading and laboratory work in relation to their specialty All the postgraduates will attend the medical sciences course A new postgraduate course in anatomy and physiology will also begin in October in the preclinical departments of St Salvator's College The director of postgraduate education is Prof R B Hunter, F R C.P E, department of pharmacology and therapeutics, Queen's College, Dundee

IRELAND

Dublin

The only postgraduate course of the University of Dublin at present available for other than Dublin graduates is that for the diploma in gynaecology and obstetrics The number of places in the course has been limited to 15 The examination for the diploma in psychological medicine is now open to graduates of other universities Last year a clinical postgraduate course, restricted to Dublin graduates, was given at the end of the long vacation, the course was very successful and a similar course will be given this year

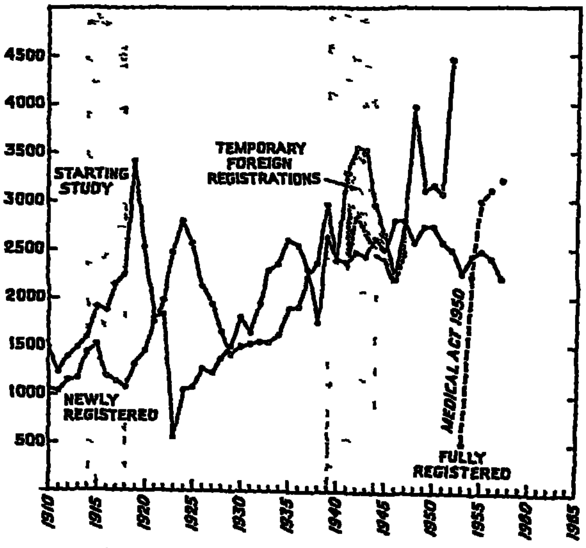
The National University of Ireland awards diplomas in public health, psychiatry, and child health

REGISTRATION

No-one is a legally qualified medical practitioner unless his name appears on the Register kept by the General Medical Council In the field of medical education the Council has a statutory responsibility for ensuring that the courses of study and examinations for any qualification conferring a title to registration do not fall below a proper minimum standard The Council, through its Disciplinary Committee, is also responsible for discipline within the profession The Medical Act, 1956, regulates the constitution and functions of the Council and the procedure of medical registration and discipline The new Act superseded a great many statutory provisions that had preceded it The Act, and Orders and Regulations made under it, provide that a person will not be eligible for full registration until he has, after passing a qualifying examination, served as a house-officer in approved hospitals or institutions for twelve months During this period he would be provisionally registered

The approximate number of second-year students admitted to medical schools in the United Kingdom and in Ireland was 2725 during 1950–51, 2565 during 1951–52, 2494 during 1952–53, 2280 during 1953, 2437 during 1954, 2485 during 1955, 2415 during 1956, and 2192 during 1957

The numbers newly registered (including Commonwealth practitioners) were in 1951, 3075, in 1952, 4493, in 1953, 2320 (507 fully registered and 1813 provisionally registered), in 1954, 4542 (2222 fully registered and 2320 provisionally registered), in 1955, 5310 (2992 fully registered and 2318 provisionally registered), in 1956, 5522 (3113 fully registered and 2409 provisionally registered, and in 1957, 5455 (3226 fully registered and 2229 provisionally registered) The totals for 1954–57 include, of course, a considerable proportion of those provisionally registered in the previous year The widening gap between the number provisionally registered and those fully registered in recent years is largely due to the



Numbers starting study and registering *

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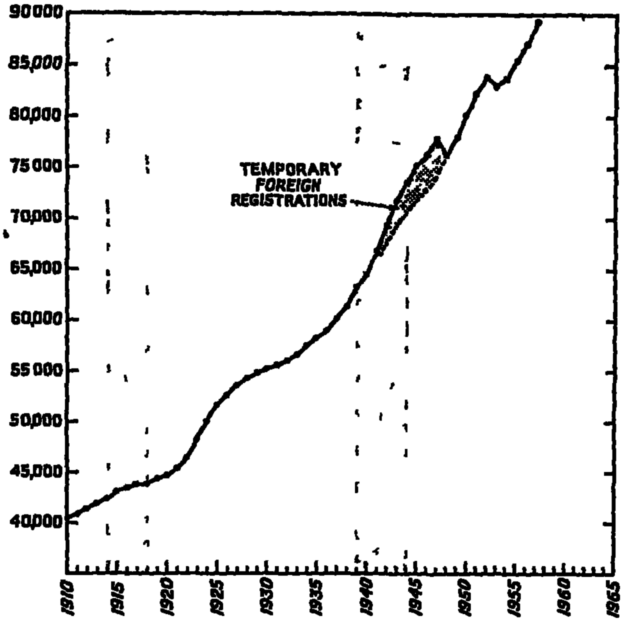
* The numbers shown as starting study are taken from the Medical Students Register up to 1938, and since then from returns made by the medical schools to the General Medical Council Both forms of notification are incomplete for certain years Starting with 1953, the figure is based on the annual examination returns and covers the calendar year instead of the academic year as formerly



Number of fully registered doctors on the Medical Register

increasing number of Commonwealth practitioners who obtain full registration, without (except in a minority of cases) first applying for provisional registration

The number obtaining provisional and full registration in 1953 was much lower than in the preceding five years This is attributable to two things (1) some people who would normally have registered in 1953 took special steps to obtain registration before the end of 1952 in order to avoid the preregistration year, and (2) the lengthening of the curriculum at certain Scottish universities meant that fewer than usual qualified and became provisionally registered in 1953 The striking increase in the number of newly registered doctors in 1952 (4493 as against 3075 in 1951) was largely due to the addition of 1452 names to the Commonwealth List in 1952 (as compared with 471 in 1951)

The Defence Services

Royal Naval Medical Service

The Medical Service of the Royal Navy affords, to medical practitioners who are attracted by the prospect of sea service and work with the Royal Navy, a wide opportunity to practise their profession in an attractive environment A background of naval tradition naturally permeates the Royal Naval Hospitals and Naval Training Establishments, as well as Her Majesty's ships Officers serving on the permanent list are encouraged to specialise in all branches of medicine, and they are given full facilities to obtain higher qualifications Courses of postgraduate study are carried out not only in naval hospitals but also at civilian teaching centres There is a wide variety of subjects comprised in the title "naval medicine", and it might often be claimed that certain of these subjects are unique They include the physiology of diving, the physical aspects of service afloat and ashore, Commando service, tropical diseases, and industrial hygiene, an important further specialty is that of aviation medicine, and a small number of Naval medical officers undergo full pilot training before undertaking duties with the Fleet Air Arm or in research establishments Furthermore, a naval medical officer is no longer concerned with the care of the sailor alone, but must also have up-to-date knowledge of the diseases of women and children so that he may attend the needs of the W R N S, members of the Q A R N N S, Naval V A D s, and the wives and children of Servicemen and Admiralty personnel serving abroad

The Royal Naval Medical Service offers a life career with service on the active list up to 55 for all officers, to 57 for surgeon captains, and to 60 years of age for surgeon rear admirals Provision is made in the regulations for counting previous experience, both service and professional All previous commissioned service as a medical officer in one of the Armed Forces is allowed to count in full, and all non-medical commissioned service is allowed to count as half Civilian hospital experience, and also experience of a special nature in private practice which is recognised by the Medical Director-General as warranting additional seniority, may be allowed to count up to a limit of seven years in all

The additional seniority will be reckoned as service for pay and promotion but not for retired pay or gratuity Leave is granted to officers at the following scales in the United Kingdom, 42 days a year, when appointed to H M Ships on general service, at the rate of 3 days a month, when on foreign service, 14 days local leave a year with a further 2 days for each month abroad on return to the United Kingdom

Entry in the first place is for a short-service commission of either three or four years which may be extended During this time application may be made for transfer to the permanent list. Medical practitioners who undertake their National Service in the Royal Navy are also eligible to apply to transfer to the permanent list The normal career for a medical officer provides for promotion to the full rank of surgeon lieutenant after one year's service, and to surgeon lieutenant-commander after a further seven years' service Surgeon lieutenant-commanders are promoted to surgeon commander by selection at about their 15th year of total service and surgeon commanders are promoted by selection to surgeon captain about their 23rd year of total service Subsequent promotion to surgeon rear admiral is by selection

Rates of pay are as follows

Rank	*Pay per annum*
Acting surgeon-lieutenant	£657
Surgeon lieutenant	£766–£1053
Surgeon lieutenant-commander	£1295–£1569
Surgeon commander	£1660–£1931
Surgeon captain	£2080–£2363
Surgeon rear-admiral	£3029
Surgeon vice-admiral	£3759

Additional allowances are granted to married officers according to rank When the officer is not accommodated or messed, additional allowances are paid

Medical officers are also eligible for allowances, in addition to the basic rates of pay, on the same scale and under the same conditions as for other officers of equivalent rank These include travelling expenses, subsistence allowance, and passages for wives and families Officers who transfer to permanent commissions after a minimum of one year's service will be paid a permanent commission grant of £1500 (taxable)

The maximum rates of retired pay in addition to terminal grants are payable to officers who complete certain specified periods of service Officers allowed to withdraw who are ineligible for retired pay will be eligible to receive gratuities

Further information may be obtained from the Medical Department, Admiralty, Queen Anne's Mansions, St James's Park, London, S W 1

ROYAL NAVAL DENTAL SERVICE

Dental officers are entered for Naval service under similar conditions to those applying to medical officers Information concerning conditions of service can be obtained from the Medical Department of the Navy, Queen Anne's Mansions, St James's Park, London, S W 1

Royal Army Medical Corps

There is, at the moment, a limited requirement for trained specialists, particularly ophthalmologists, otolaryngologists, and radiologists In the main, however, the R A M C seeks applications from young recently qualified practitioners

Non-specialist Career

66% of medical officers will be employed on general practitioner duties After attending the junior officers' course at the Royal Army Medical College, they serve 2 years as officer in medical charge of a unit with concurrent part-time duties in a military hospital where they become conversant with the soldier and his environment, the objects of the

Army, and the requirements from its medical service in peace and war They will, later, serve overseas where, as a regimental medical officer or in charge of troops and families, a reception station or small hospital, or in field medical units they will be able to study the causation, prevention, and treatment of tropical diseases, the effects of climate, &c On their return, they attend the senior officers' course, the first 2½ months are spent in study at the Royal Army Medical College, Millbank, and the next 3 months in a special postgraduate course at a London teaching hospital At this stage officers may opt to remain at general medical duties or take up field training or junior staff appointments For the more senior ranks the requirements are a sound background of clinical and preventive medicine to meet their advanced responsibilities in the administration of the Army Medical Services in peace and war

Specialist Career

Specialists are, subject to professional proficiency, employed on specialist duties up to the rank of colonel Thereafter they may serve in this rank up to the retiring age of 57 or may be selected for promotion to brigadier either in a specialist or non-specialist capacity The process of selection for specialist training is carried out after the junior officers' course, those applicants who are most successful in the course examination being accepted Those accepted are provided with excellent opportunities to obtain higher qualifications and specialist experience

Postgraduate Training

There are liberal arrangements for specialists and non-specialists to undergo postgraduate training throughout their career

Employment after Retirement

All suitable medical officers (specialist or non-specialist) may be employed up to the age of 65 in appointments specially set aside for retired officers Non-specialists are employed on general practitioner or medical administrative duties and specialists on specialist duties

Conditions of Service

As conditions of service greatly affect a wife, married practitioners considering an Army career are advised that their wives should discuss these conditions with Army wives who have served at home and overseas

The *overseas tour* is of 3 years' duration Families of officers aged 25 or over can, in the case of most overseas stations, accompany the officer by sea or air Local allowances are paid in certain overseas areas where the cost of living is greater than in the United Kingdom Schools are normally available locally, and in the case of those with children between 11 and 18 years left in the United Kingdom a tax-free education allowance of up to £75 per year for the first child, £100 for the second child, and £125 for the third and subsequent children, is paid if they attend boarding-school, or £35 a year if they attend day school and are placed in the care of a guardian These allowances will also be payable for children undergoing vocational and technical training The facilities for sport and leave travel vary but are usually very good

A *home tour*, spent in U K or North-West Europe, lasts at the moment 4–5 years As a rule there is no difficulty in obtaining family accommodation or arranging schools The education allowance referred to above is, however, subject to income-tax in the case of those serving in U K, but not in North-West Europe

It is the Army policy that all ranks should be given some months' warning of an impending move This is done as much as possible but cannot always be achieved—for example, the posting of an officer after the senior officer's course may be influenced by his performance on the course and cannot be decided beforehand, and emergencies may necessitate a sudden chain of appointments and reliefs

Married officers over 25 years of age are allowed, subject to certain conditions, travel at public expense for their family from duty station to duty station on posting, or to a selected place of residence if accommodation is not available at the new duty station Those serving on a commission of three years or over may also be eligible for refund of furniture-removal expenses, disturbance allowance of £40 or £20 (according to the type of accommodation occupied) designed to cover incidental expenses when the family are required to move for service reasons, and, when serving overseas with their family, refund of furniture-storage charges

Family accommodation provided by the Government is at a reasonable rent—furnished accommodation for a major is, for example, £180 per year

The comradeship of the Army extends to wives and children, but the wives of those interested will find out about this and the advantages and disadvantages of an Army life far better from other Army wives

Conditions of Commissioning

The normal maximum age is 33 but allowance is made for those who have previously held commissioned rank in H M Forces on full pay An antedate, counting towards pay and promotion, may be allowed for 2 years spent in civilian practice or hospitals An additional period of up to 5 years may be allowed for specialist appointments held An allowance is also made for previous commissioned service on full pay This antedate counts towards the "reckonable service" mentioned below

Promotion and Pay

Details are given in the accompanying table In addition the following are payable

On appointment to a permanent commission, a taxable grant of £1500

Officers are entitled to an initial outfit allowance in addition to certain free issues of clothing, so that they may provide themselves with the authorised scale of uniform without expense to themselves In addition, a tropical-kit allowance is granted to officers on first posting to stations for which tropical kit is authorised These allowances are tax-free Relief from income-tax on necessary expenditure on maintenance of uniform, estimated at £40 a year, is admissible annually

Junior specialist pay	£73 per year
Senior specialist pay	£219 per year
Qualification pay (for Staff College graduates)	£63 to £127 per year

PROMOTION AND RATES OF PAY OF R A M C MEDICAL OFFICERS

Rank	Promotion	Pay	Marriage allowance (age 25 or over)			Ration allowance
			In married quarters	Out of married quarters	Under 25	
		£	£	£	£	£
Lieutenant	—	657	355	410	219	106 (not taxable)
Captain	1 year's reckonable service	766–1058	355	410	219	
Major	8 year's reckonable service	1295–1569	401	456	—	
Lieut -colonel	By selection after about 17 years	1660–1934	456	511	—	
Colonel	By selection after about 23 years'	2080–2244	456	511	—	
Brigadier	By selection	2354	520	574	—	
Major-general	By selection	3029	611	666	—	
Lieut -general	By selection	3759	611	666	—	

Retired Pay, &c

For less than 20 years' qualifying service, there is a tax-free gratuity rising from £1000 at 10 years' service to £2800 at 19 years' service

Pensions are payable as follows on retirement at the ages and with the reckonable service stated

Major	£625 for 22 years' reckonable service at 53 years, plus lump-sum grants of £1875
Lieut -colonel	£800 for 24 years' reckonable service at 55 years, plus lump-sum grant of £2400
Colonel	£1000 for 26 years reckonable service at 57 years, plus lump-sum grant of £3000
Brigadier	£1150 for 28 years' reckonable service at 59 years, plus lump sum grant of £3450
Major-general	£1400 for 30 years' reckonable service at 60 years, plus lump-sum grant of £4200
Lieut -general	£1600 for 30 years reckonable service, on completion of appointment, £4800

Deductions are made in the case of an officer whose reckonable service is less than stated above or who retired voluntarily 2 or more years before his compulsory retiring age

Retired-officer Appointments

These may be held from the date of retirement until the age of 65 The annual salary ranks from £1130 to £1400, in addition to pension

Further information may be obtained from the Assistant Director-General, The War Office (A M D 2), London, S W 1

ROYAL ARMY DENTAL CORPS

Registered dental surgeons of British nationality or citizens of the Irish Republic who are liable for service under the National Service Act may apply for short-service commissions for not less than 3 years on the active list, with a reserve liability up to 8 years from the date of their appointment Those (both men and women) *who are not liable for service may apply for short-service commissions* for varying periods of between 2 and 8 years on the active list An antedate of seniority counting towards increments of pay and time promotion may be granted for postgraduate civil professional experience, previous commissioned service in the Armed Forces is also taken into consideration A tax-free gratuity is payable Officers or dental surgeons (male) may be appointed to permanent commissions *direct or at any time during the short-service or National-Service* engagement Until further notice, those so appointed will be paid a special grant of £1250 (taxable) after one year's satisfactory service as dental officers The period of their short-service commissions will reckon towards ultimate retired pay and service gratuity, but will not entitle them to short-service gratuities Dental surgeons who are eligible to apply may obtain full particulars and application forms from the Under-Secretary of State, The War Office (A M D 6), London, S W 1

Royal Air Force Medical Branch

The Royal Air Force offers an attractive career to fully registered men and women medical practitioners who are British subjects or citizens of the Irish Republic Normally, the upper age-limit for applicants is 33, but older applicants may be considered Appointment is usually to short-service commissions for three, four, five, or six years in the first instance, each of which may be extended to complete a maximum period of eight years' service Exceptionally, suitable candidates may be appointed to permanent commissions direct from civil life Short-service officers may apply for permanent commissions at any time during their service

Medical officers come into contact with flying and air evacuation of sick and wounded, as well as the clinical specialties and the treatment of Service families There are, in addition, opportunities in aviation medicine, hygiene, and industrial medicine

For regular officers, antedates of seniority may be admissible for recognised civil experience These antedates reckon towards pay, seniority, and promotion The normal rank on appointment is flying-officer, with promotion to flight-lieutenant after one year's reckonable service, to squadron-leader after eight years' reckonable service, and to wing-commander after seven years' satisfactory service in the substantive rank of squadron-leader Officers recognised as R A F specialists will be promoted to the rank of group-captain after eight years' satisfactory service in the substantive rank of wing-commander, and to ranks above group-captain by selection Promotion to group-captain and above for non-specialist officers will be by selection

Officers serving on permanent commissions may be allowed study-leave with full pay and allowances to take approved postgraduate courses, for which tuition fees on an approved scale may be granted Officers having experience or aptitude in a specialty may be employed on specialist duties and subsequently earn recognition as junior specialists with additional pay of 4*s* per day and as Royal Air Force specialists with additional pay of 12*s* per day Non-specialist medical officers below the rank of group-captain will be awarded additional pay of 4*s* per day on gaining a registrable diploma in public health, industrial health, or tropical medicine, provided that in each instance the prescribed period of study occupied an academic year

Officers appointed to permanent commissions will receive a grant of £1500 (subject to income-tax) after one year's satisfactory service and they will be entitled to retired pay and other benefits after completion of service Short servic officers will, on completion of their commissions, be paid a *tax-free gratuity at the rate of £200* for each year of satisfactory service Arrangements exist to preserve their superannuation *rights under the National Health Service (Superannuatio* Regulations, 1950

Further information can be obtained from the Und Secretary of State for Air, Air Ministry, M A 1, 1–6, Tavisto Square, London, W C 1 (Euston 5040, ext 310)

ROYAL AIR FORCE DENTAL BRANCH

Commissions are available in the Royal Air Force Dental Bran to candidates of either sex who possess a degree or licence in den surgery of a British university or licensing board, and who a registered under the Dental Act in force in the United Kingdo Dental officers in the Royal Air Force have plenty of scope for the aspects of dentistry in a branch which trains its own technica and *maintains its own laboratories* under *senior dental office* Dental officers serving on short-service or National-Service co missions may apply at any time for appointment to permanent co missions The length of the period on a short-service commiss and the period required in the reserve on its completion is the sa *as for medical officers Similarly, dental surgeons may be gran* permanent commissions if they can complete at least twenty yea service qualifying for retired pay Previous commissioned serv counts for antedate of seniority rank on appointment, and terms promotion the same as for medical officers, while antedates for ci experience in a recognised professional appointment are given on t following basis, subject to a maximum antedate of seven years f *such experience first four years, in full, any later experience,* in ha Candidates who hold specialist appointments may be allowed have their civil experience assessed on a different basis, but with the same maximum of seven years A tax-free gratuity, at the rate £170 a year for each year of satisfactory active-list service, is payab *to short-service* officers on transfer to the *reserve* Dental office appointed to permanent commissions are encouraged to pursue the studies in postgraduate research and may be allowed up to seve months' study leave on full pay and allowances to take approv postgraduate courses Until further notice, a grant of £1250, subje to income-tax, will be made after one year's satisfactory commission service in the dental branch, to officers appointed to permane *commissions Short-service or permanent-commission* officers wh have the appropriate higher qualifications and the requisite experienc may be recommended for specialist appointments Further informa tion may be had from the Under-Secretary of State, Air Ministry M A 6, 1–6, Tavistock Square, London, W C 1 (Euston 504 ext *106*)

Health Services at Home

PUBLIC HEALTH

AMONG the divisions of the nation's health services, *publi* health ranks next in size and importance to the general practitioner *and hospital services and it offers a* satisfactory career to the young doctor keen to work for the welfare of the *community as well as for the individual*

Under the National Health Service Act of 1946, councils of counties *and* county boroughs *were* designated "local health authorities" and had conferred upon them, and through them upon their medical officers of health, wide responsibilities for the provision of personal health services These include a duty to provide clinics and other services for mothers and young children, domiciliary *midwifery*, home nursing, *domestic help* health visiting, immunisation, vaccination, and ambulanc services Wide powers are also given to these *authorities* to prepare and administer schemes for the prevention of diseas *and for the care and aftercare of sick persons* Recently, new concepts have been developing in the mental-health services *and there* will be considerable expansion in local-health authority responsibilities as the result of the recommendations in the report of the Royal Commission on the Law relating to Mental Illness and Mental Deficiency In most counties and county boroughs the medical officer of health *is principal* school medical officer and is thus responsible for the preventive health services covering children of all ages In some areas further coordination has been secured by placing the *authority*'s socia welfare services also under the medical officer of health. Under the Local Government Act of 1958, many of these health and welfare functions may now be delegated to the larger county district authorities.

In county boroughs, boroughs, and urban and rural districts, the medical officer of health is responsible for environmental hygiene. In contrast with the early days of public health when the medical officer of health was personally concerned with the execution of many sanitary duties, health departments are now organised to free him from much of the detailed work, which is performed by trained lay officers, or even transferred to the care of other departments—as in the case of water-supply and sewerage disposal. Naturally, the extent of this devolution of responsibility varies widely, and in rural areas problems of water-supply and sanitation are still a major concern of the medical officer of health. The supervision of housing conditions is also a responsibility of the health department. All this work remains under the general control of the medical officer of health, and he must supervise the purity of water-supplies even though their production is not his concern. Though less concerned with detailed work, supervision must be far wider than that exercised by his predecessor of a hundred years ago.

Control of infection has always been one of the principal functions of the medical officer of health. Laboratory workers have made great advances in the identification of species and strains of bacteria and viruses and new techniques applied to epidemic control have given the medical officer of health an instrument of precision in much of his epidemiological work. The application of specific prophylactic measures against various acute infections is now an important function of all health departments. Drastic reduction, if not the complete extinction, of many important infectious diseases has become a feasible target for all health departments.

Recent developments have increased the opportunities for the young medical officer to obtain a comprehensive training in public health. In the larger towns there are now more posts of senior-medical-officer grade, and in counties, schemes of divisional administration have been evolved. The work of the medical officer of health to a number of county district authorities is often combined with an appointment as assistant or divisional county medical officer of health. The holder of such a post obtains a detailed knowledge of the community under his care, and, while retaining a high degree of individual responsibility, he suffers none of the disadvantages of rural isolation.

A sound clinical background is an essential qualification for the new entrant and a course leading to the diploma in public health should be taken at an early stage since this qualification is necessary for anyone seeking an appointment as a medical officer of health. For doctors engaged in clinical preventive medicine a *diploma* in child health, in obstetrics and gynæcology, or in psychological medicine is an advantage.

Individual progress in a public-health career depends largely, if not entirely, upon the doctor's personal qualities, for, as adviser to his authority, the reputation of the medical officer of health depends on the soundness of the advice he gives. Quite apart from his statutory functions, he has an important part to play in promoting the health education of the community, and in helping to secure full coordination between the branches of the health service in his area. He is assisted by the regular liaison meetings, which are held in most regions, between the hospital boards and the county and county borough medical officers of health. Most hospital boards rely on the medical officer of health to determine the urgency of the social grounds for admitting patients to hospital, especially in maternity cases and when considering the chronic sick. Some medical officers of health have been appointed as members of hospital medical advisory committees or of hospital management committees, and, through the National Health Service Act, a closer relationship with the general-practitioner services has now become possible.

INDUSTRIAL MEDICAL SERVICES

INDUSTRIAL or occupational medicine is gradually taking its proper place among the branches of medicine. Whatever may be the merits or demerits of a classical education, it is certain that the social stigma placed by the ancient Greeks on the mechanical arts and trades led to the neglect of the working man in ancient medical practice and of the occupational diseases by medical science. Even now the influence of the classics on this aspect of medicine has not been entirely dissipated, and it is a rare physician who goes fully into the details of his patient's occupation and tries to estimate its effect on his health. This is surprising because there is no study more fascinating than that of the physical and mental reaction of man to his environment. Industrial medicine has both preventive and curative aspects but it is generally regarded as a branch of preventive medicine, and of public health in its wider sense, or even of the loosely defined concept of social medicine.

In November, 1954, the Minister of Labour and National Service announced in the House of Commons that he had decided to take steps to stimulate the further development of industrial health services in work-places covered by the Factories Acts. He later set up a standing industrial health advisory committee to carry out a review to ascertain where industrial health services most needed to be extended. Two pilot surveys have been undertaken—one in Halifax and the other in Stoke-on-Trent—and the results of the Halifax survey have now been published.

It is to be hoped that the deliberations of the industrial-health advisory committee will lead to the creation of more posts for doctors interested in occupational medicine. These posts fall into various categories, such as those in the Civil Service, the nationalised industries, research organisations, the universities, and factories. But, though the importance and opportunities of industrial medicine are increasingly recognised, it cannot yet be said that in salary or prospects the openings in this work are always as favourable as those in the National Health Service. For industrial posts within the Civil Service, the prospects have improved slightly as a result of the Royal Commission on the Civil Service, but even at present this service does not offer enough senior appointments to assure promotion to all who earn it. Moreover, as things are at present, the top posts in the medical Civil Service are often filled by doctors who previously held appointments outside the service, and this is a discouragement to those who are contemplating entry through the basic grade.

The appointments as medical officers to factories and other industrial organisations vary in attractiveness, both as regards opportunities and salaries. In some the conditions and prospects are good, and the British Medical Association has laid down a scale of minimum salaries.

The main Government department supervising the health of industrial workers is the Factory Department of the Ministry of Labour and National Service. This department, which up to 1940 worked under the Home Office, dates from 1833 and administers the Factories Acts (1937 and 1948) with regulations on accident and sickness prevention, hours of work, amenities, and canteens. The inspectorate numbers about 412, of whom 18 are doctors. Members of the department, whether lay or medical, take part in the activities directed towards the prevention of illness and maintaining the health of the factory population. The medical inspectors are stationed in London, Birmingham, Sheffield, Liverpool, Cardiff, Manchester, Glasgow, and Leeds, and from these centres they are able to deal with factory health and conditions in any part of the country. Under them 1750 general practitioners give part-time service as appointed factory doctors (previously called examining surgeons), examining all young entrants into industry, and periodically all those engaged in specific dangerous processes. In addition there are about 400 doctors employed whole-time in factories or groups of factories, and about 3000 (may be more) in part-time work. An interesting development in recent years has been the setting-up of medical services for looking after workers on trading estates. Three such schemes, at Slough, Hillington, and Bridgend are well established and others are projected to serve the trading estates at some of the "new towns" One such service is now in operation at Harlow in Essex It has been a common criticism of the industrial medical services that the workers at small factories are not catered for, and these group services might well form a model for a national service It is well to bear in mind, however, that even in factories where there are no doctors a close watch on conditions is maintained by the Factory Department

Apart from the Factory Department, other Government departments deal with various aspects of the industrial medical services For instance, the Post Office, which employs more workers than any other department, has had a medical service since 1855, and since it deals with engineering and manual workers in addition to office staffs, it is partly an industrial medical service The Post Office medical staff is now directed by the chief medical adviser to the Treasury, who has in addition a staff of 15 doctors which deals with the health problems of the Civil Service The inspectorate of the Ministry of Fuel and Power has a medical section with a few full-time medical inspectors The National Coal Board provides a comprehensive industrial medical service and research programme for the industry which now has a large staff of whole-time doctors The Ministry of Supply Medical Service with 40 doctors deals with the health of the workers in the Royal Ordnance factories, and in the research stations The Ministry of Pensions and National Insurance has a medical staff both at headquarters and in the regions, which advises on compensation for industrial injuries as well as for other causes of ill health The former silicosis and asbestosis board is now a part of the medical service of the Ministry On the staff of the pneumoconiosis medical panels, as they are now called, are some 37 whole-time medical officers who deal with the diagnosis and certification for compensation of cases of silicosis, asbestosis, and some other forms of pneumoconiosis They also carry out periodical medical examinations of workers engaged in some scheduled occupations in which cases of pneumoconiosis are likely to arise The centres from which the panels work are Swansea, Cardiff, London, Manchester, Sheffield, Stoke-on-Trent, Bristol, Birmingham, and Edinburgh Some of the newly nationalised industries have established medical services—for example, the London Transport Executive, a part of the British Transport Commission The London Transport Executive employs a chief medical officer with 9 full-time doctors The National Dock Labour Board also has a medical service consisting of 7 full-time medical officers and 1 part-time medical officer Some, but not all, of the regional boards of the nationalised gas industry have appointed whole-time and part-time doctors to look after the health of the workers

In addition to investigations and research into industrial diseases conducted by medical inspectors of factories, mines medical officers and works doctors, much fundamental research into environmental conditions has been carried out by the various departments of the Medical Research Council Clinical and field studies made under the ægis of the council's industrial pulmonary diseases committee include inquiry into the pneumoconiosis of coalminers and the byssinosis of cotton workers The London Hospital department for research in industrial medicine was established in 1943, and a few years later, in conjunction with the Ministry of Fuel and Power, a bureau for research into pneumoconiosis and other diseases was set up Other units of the council dealing with industrial health include the toxicological research unit at Carshalton, the groups for research in industrial and applied psychology in Cambridge, and London, and the industrial injuries and burns research unit at the Birmingham Accident Hospital There is also a unit for research on climate and working efficiency at the department of human anatomy at Oxford, a social medicine research unit at the London Hospital, and a statistical research unit at the London School of Hygiene and Tropical Medicine Problems on the health aspects of atomic energy are being dealt with at Harwell Research into industrial health matters is also being undertaken by the university departments mentioned below

The Institute of Social Medicine at Oxford, which works under a joint board, also undertakes investigations into various aspects of industrial health At the London School of Hygiene and Tropical Medicine, the Rockefeller Occupational Health Unit was established in 1956 University chairs devoted to industrial or occupational medicine have been set up at Manchester and Durham The chair of social medicine at Birmingham includes industrial medicine within its terms of reference and the University of Sheffield has appointed a professor of social and industrial medicine Students are likely to hear more about these subjects in their undergraduate courses Postgraduate courses are held in London, Birmingham, Sheffield, and Manchester, and occasionally at other centres Diplomas in Industrial Health (D I H) have been instituted by the Society of Apothecaries, the Conjoint Board of the Royal Colleges of Physicians and Surgeons, and the Faculty of Physicians and Surgeons of Glasgow The Association of Industrial Medical Officers was formed some years ago by doctors interested in industrial health, and branches have been established in various parts of the country, the *British Journal of Industrial Medicine* is sponsored by this association in conjunction with the British Medical Association The association has also since April, 1951, published a quarterly journal, called the *Transactions of the Association of Industrial Medical Officers*, which is devoted to the dissemination of information about the practical arpects of industrial medicine rather than to original research

PRISONS AND BORSTAL INSTITUTIONS

THE medical service is a part of the general-service class of the medical Civil Service, under the immediate control of the Director of Medical Services at the Prison Commission The work is mainly clinical and the medical officer is responsible for the physical and mental welfare of the inmates, a responsibility which extends to a general oversight of the hygiene of the establishment in which he is working The service is expanding to meet the needs of a rising inmate population and the increased demands of present-day methods It offers an attractive career to medical practitioners who are interested in the various problems connected with crime and the understanding and treatment of criminals The medical and surgical cases seen are comparable with those met with in outside practice The various establishments have their own hospital accommodation, a large prison, for example, may well have a hospital with up to 100 beds The doctor in a prison or borstal is a member of a team whose efforts are directed towards the rehabilitation of those committed to its charge On the medical side the aim must be not only to attend to ordinary day-to-day medical care but to discover, and if possible to remedy, disabilities and maladjustments which hinder the training of the offender and make it more difficult for him to regain a place among law-abiding citizens Although not a member of the National Health Service the prison medical officer maintains a close liaison with the hospital and specialist facilities of that service, and thereby gains much both for his patients and himself by contact with advances in medical knowledge and procedures

There are now over seventy establishments under the control of the Prison Commissioners, and as is to be expected, they vary very much in their size and purpose depending on the class of inmate, and the medical requirements differ accordingly At the larger establishments the medical work is in the hands of whole-time medical officers, whereas the small institutions are served by part-time doctors who are usually local general practitioners The more important prisons may have as many as four or five full-time medical officers, together with psychologists and psychological testing assistants At a few prisons there are also psychiatric social workers Principal and senior medical officers have advisory and other duties in connection with small groups of establishments The medical officer is called upon to make medical and psychiatric reports to the Commissioners from time to time In remand prisons the preparation of reports to court and the giving of verbal evidence, particularly in regard to the mental condition of offenders, are important aspects of the work Postgraduate experience in psychiatry is therefore an advantage. Surgical and psychotherapeutic units are established at selected centres where the work is undertaken mainly by visiting specialists working on a sessional basis and in close association with the regular medical staff

The national scales, in accordance with the general Civil Service scales, are

Medical officer*	£1690 rising by seven annual increments to a maximum of £2300
Senior medical officer	£2650
Principal medical officer	£2950

* Linked to aged 35 minus £45'50 for each year below that age, and plus one increment for each year above 35 up to 40 years of age.

Officers serving in London receive £40 to £50 a year more, and until 1962, officers in certain provincial areas receive slightly less than the national rate

The appointments are pensionable, without contributions being required, and on retirement normally a pension and lump-sum gratuity are payable There is also a contributory widows' and children's pension scheme. Pensionable service under the National Health Service and established Civil Service may be aggregated for pension Unfurnished quarters, when available, are provided at a moderate rental

Permanent appointments are made by the Civil Service Commission, 6, Burlington Gardens, London, W 1, to whom inquiries for such appointments should be addressed On occasion temporary full-time appointments are available and for such appointments as well as for part-time appointments particulars can be obtained from the Prison Commission, Horseferry House, Dean Ryle Street, London, S W 1

Services Abroad

HER MAJESTY'S OVERSEAS CIVIL SERVICE MEDICAL BRANCH

THE medical departments of the Governments of the territories overseas for which the Secretary of State for the Colonies is responsible offer a wide range of openings to the right type of doctor There is a large field of medical opportunity in these territories and whatever political future they may have, there is no doubt that they will require the help and advice of British medical men for many years to come The work of a medical officer overseas is many-sided and requires a doctor of all-round capabilities There is an immense and fascinating field of clinical work, but the doctor must be prepared to occupy himself with a good deal of public health and social medicine. He must, of course, be ready to work with non-European colleagues and although the actual conditions of life and work vary greatly from territory to territory, life abroad has many pleasant features and often gives more scope for individual responsibility than life in Britain.

Vacancies occur in many parts of the world The greatest number is in tropical Africa Candidates must ordinarily be British subjects holding medical qualifications registrable in the United Kingdom, and should normally be under 45 years of age In some territories permanent appointments are available Candidates selected for permanent appointments become members of the medical branch of Her Majesty's Overseas Civil Service Many future appointments are likely to be made on the basis of short-term contracts, usually renewable, and carrying a generous gratuity on termination Doctors in the National Health Service may take temporary appointments overseas up to six years without loss of pension rights

In the first instance medical officers are usually appointed for general duties, which require a balanced outlook upon both preventive and curative medicine Such duties often involve the charge of a district hospital' and responsibility for the medical administration of a district Although many officers are employed on clinical duties in the large hospitals, some posts are purely concerned with public-health work and for these the possession of the D P.H is generally necessary

There are many specialist appointments which, if permanent, are normally filled from within the service by officers possessing the necessary aptitude, experience, and qualifications, wherever they may be serving Senior administrative appointments are filled by the promotion of serving officers whose opportunities are not necessarily confined to the territories in which they are serving.

Officers possessing qualifications or experience in pathology can be considered for appointment to the laboratory establishments Workers in the laboratories carry out pathological and biochemical examinations for clinical, forensic, and public-health purposes

There are a number of posts for women doctors, particularly for those with special experience in obstetrics, school health, child welfare, and nutrition, although their employment is not necessarily confined to these subjects

Salaries vary considerably from territory to territory in accordance with local conditions Some existing salary scales for medical officers are

	£
Nigeria	
Federation	1128–1950
Northern	1212–1950
Eastern	
Western	1056–1950
Sierra Leone	1248–2046
Gambia	1128–1950
Kenya	1284–2115
Uganda	
Tanganyika	
Hong-Kong	1305–2484
North Borneo	1470–2324
Sarawak	
Fiji	F1050–2000
Jamaica	900–1600

Specialists and senior administrative officers receive super-scale salaries ranging broadly from £2300 to £3075 and in many territories there are cost-of-living allowances and allowances for children's education. Passages are free and quarters are usually provided at a low rental Leave is generous and officers pay income-tax at local rates, mostly much lower than those in the United Kingdom Private practice is allowed to a limited extent in some territories, according to local regulations

It is impossible here to give more than a brief outline of medical appointments in the territories overseas and candidates are advised to seek fuller information from the Director of Recruitment, Colonial Office, London, S W 1

FEDERATION OF RHODESIA AND NYASALAND

THE Federal Government administers the health services of Southern Rhodesia, Northern Rhodesia, and Nyasaland. The rates of pay for full-time officers are

	£
Secretary for Health (1)	3500
Directors of medical services (3)	3050
Deputy directors of medical services (3)	2850
Directors public health laboratories (4)	2750
Ophthalmologists (3)	2750
Medical superintendents (9)	2750
Senior medical officers (9)	2750
Radiologists (3)	2750
Specialists (surgery medicine psychiatry, anaesthesia tuberculosis leprology) (19)	2750
Provincial medical officers of health (4)	2750
Medical superintendents (3)	2450
Radiologists (4)	2450
Pathologists (3)	2350
Medical superintendents (5)	2350
Medical superintendents (3)	2250
Medical superintendents (2)	1925–2050
Medical officers of health (8)	1775–2050
Government medical officers (144)	1350–2050
Schools medical officers (2)	1350–2050

Government medical officers are permitted private general practice in the rural areas, the value of this varies considerably and may reach £1000 a year, but where the net receipts fall below £200 a year a payment is made to bring the total receipts to that figure In other areas no private practice is allowed and an allowance of £200 a year is paid in lieu Medical officers of health who have not been promoted before reaching the top of their scale are paid a non-pensionable allowance at the rate of £50 a year for each year they remain at the top of their scale up to a maximum of £200 per annum Medical superintendents and most specialist officers are allowed consultant practice, the cash value of which is not great The duties of Government medical officers include the supervision of general and special hospitals and African clinics and dispensaries, medicolegal work, and preventive medicine They also include attendance on those officers of the Federal and Territorial Governments and others who are entitled to free medical attention, such as boarders in Government schools and prisoners These duties thus provide a wide field for clinical work and for the investigation and treatment of African diseases Generous provision is made in the regulations for the grant of study leave with pay to officers who wish to attend approved postgraduate courses in order to obtain additional qualifications

Vacancies are normally advertised, but where possible the more senior posts are filled by promotion within the service Further details may be obtained from the Secretary to the High Commissioner for Rhodesia and Nyasaland, 429, Strand, London, W C 2

MEDICAL MISSIONARY SERVICE

CHRISTIAN medical men and women who wish to offer their services where the need is greatest will find opportunities in medical missionary work There are university medical schools, central and rural hospitals, and many opportunities for public-health work and research Christian missions in India and Pakistan have helped to maintain high ethical and professional standards, and have specialised in nursing and medical education In Africa they have pioneered rural health services and the training of nurses, midwives, and subordinate staff In many parts of the world the work is becoming integrated with the government services though still maintaining its identity For undergraduates pledged to this service there are hostels in London and Edinburgh After qualification, a period of eighteen months or two years in resident appointments is advised for all and also special diplomas or higher degrees for some Under certain circumstances exemption is given from National Service Special missionary training is required by some societies Service is for terms from eighteen months to five years, according to the country and climate, there are opportunities for postgraduate study during furloughs Offers for life service are preferred, but short terms are considered Financial rewards are not high but vary with need Passages are free and quarters provided For long-term service many societies have pension provision Help is given with children's educational costs Applications from students or qualified men and women should be made either to the secretary of one of the denominational or interdenominational missionary societies, or through the local branch of the Student Christian Movement or the Inter-Varsity Fellowship, or to the Chairman, Medical Advisory Board of the Conference of British Missionary Societies, Edinburgh House, 2, Eaton Gate, London, S W 1

Other Information

THE MEDICAL RESEARCH COUNCIL

THE Medical Research Council, originally established in 1913 as the Medical Research Committee, is appointed to administer the funds provided annually by Parliament for the promotion of research in medical science The council is under the general direction of a committee of Privy Council, consisting of the Lord President as chairman and the Ministers in charge of the principal departments concerned with questions of public health at home and overseas The Lord President is the Minister responsible to Parliament for the council's work The members of the council, appointed by the committee of Privy Council normally for a period of four years, are twelve in number Nine of these are chosen for their scientific qualifications, of the remaining three, one must be a member of the House of Lords and one a member of the House of Commons

Although its funds are largely provided out of the Parliamentary grant-in-aid, the council is not a Government department and its staff are not Civil Servants, its constitution gives it full liberty to pursue an independent policy, and enables it to foster effective relations between science and the State, unrestricted by territorial or departmental limitations of function The council maintains close touch with the Government departments having responsibilities for public health, collaborates freely with its sister research organisations, the Department of Scientific and Industrial Research and the Agricultural Research Council, and has direct relations with similar organisations abroad

The council supports research in two main ways by employing its own scientific staff and by a scheme of grants and training awards which it makes available to workers elsewhere for specific purposes The council's annual report, published by H M Stationery Office, gives an account of the work in progress under its auspices

The council's scientific staff, with technical and other assistants, work in one major institute—the National Institute for Medical Research, Mill Hill, London, N W 7—and in some seventy research units or groups of varying size, or in some cases as individually attached workers, in universities and hospitals mainly in the United Kingdom but also in certain colonial territories The council also provides the major portion of the finance of the Institute of Cancer Research in the Royal Marsden Hospital, London, S W 3

The work of the National Institute for Medical Research, which is the largest of its kind in the Commonwealth, is designed to cover as wide a field as possible in basic non-clinical medical research, it has separate divisions of biochemistry, organic chemistry, chemotherapy, bacterial physiology, physiology and pharmacology, human physiology, immunology, experimental biology, bacteriology and virus research, biophysics and optics, biological standards, and engineering The council's research units and groups are housed, by mutual agreement, mainly within university or hospital departments

The close association of most of the council's establishments with universities and hospitals is valuable from many points of view, and especially in the opportunities it provides not only for collaboration in joint schemes of research but also for informal day-to-day discussions on scientific problems of common interest Members of units and of the external staff accommodated in university departments are often given honorary university appointments and participate to a limited extent in teaching, while in appropriate cases members of clinical units hold honorary hospital appointments In accordance with the recommendations, in the *Report on Clinical Research in Relation to the National Health Service*,[1] arrangements have been made by the council, in consultation with the Health Departments and with the advice of the Clinical Research Board, for the further development of research in this field

The interests of the council and of the universities are necessarily closely aligned in the research field but they do not merely duplicate each other The work of the council is complementary to that of the universities and under the terms of its constitution it is particularly well placed to explore new fields as they come to light and to develop new subjects rapidly on a large scale

The council's aim is to provide the opportunity for careers equivalent to those offered in the universities to men and women of equal ability and experience Its salary scales are based on this principle and approximate closely to the various grades of university appointments, the director of a council unit normally being considered to be of professorial status For the most part salaries are not fixed in relation to particular posts, but rather with reference to the ability and responsibilities of the individual promotion to a higher grade may accordingly be made without change of post The council's staff number about 2100, of whom some 700 are scientific staff and about one-half of these medically qualified.

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[1] H.M Stationery Office, 1953

Appointments to the scientific staff are made on the recommendations of the director of the establishment concerned, normally for three or five years in the first instance. Later, when an adequate degree of seniority has been attained, the council may express its intention of continuing employment until the normal retiring age of 60, with the possibility of extension to 65. Superannuation provision is made for most appointments.

PUBLIC HEALTH LABORATORY SERVICE

On behalf of the Ministry of Health, the council have administered the Public Health Laboratory Service since 1939 when it was originally set up as an emergency service. There are over 60 separate laboratories in England and Wales. In addition to their routine duties, members of the staff of the service, whose salary scales are normally equated with those of the National Health Service, undertake research in bacteriology and epidemiology. The service also maintains a number of special laboratories which act as reference centres for particular infections, and are engaged largely in research.

The following booklets covering various aspects of the council's activities are available on request to the Secretary, Medical Research Council, 38, Old Queen Street, Westminster, London, S.W.1: Constitution and Functions, Careers in Medical Research, Research Grants.

MEDICAL PRACTICES ADVISORY BUREAU

WHEN the National Health Service Act came into force, the traditional procedure for entry into general practice was considerably modified—particularly by the abolition of the sale and purchase of goodwill. It soon became apparent that there would be a need for some central source of information which could give advice to practitioners seeking openings, to those desiring to transfer from one area to another, and to those seeking to set up in single-handed practice. It was felt that advisory functions of this kind should be undertaken by a body which was not linked directly or indirectly with central or local government but whose status and resources were such as would enable it to establish and maintain effective liaison with executive councils, local medical committees, and the Medical Practices Committee, and at the same time to command the confidence of the profession. To meet this need the Medical Practices Advisory Bureau was established at the end of 1948 as a department of the British Medical Association, under the direction of a member of the medical staff of the association.

The functions of the bureau are twofold: firstly, to maintain an information service about openings in the various fields of medical practice and to introduce partners, assistants, and locums; and, secondly, to advise on individual and personal problems associated with entry into and the conduct of medical practice. A great deal of advice is sought on the various forms of contracts and agreements between practitioners. Although it is not the function of the bureau to give legal advice there are many questions concerning partnerships and assistantships where the advice of a doctor with experience is needed, as well as that of a lawyer. All doctors are welcome to seek the advice of the Bureau, at B.M.A. House, Tavistock Square, London, W.C.1, or any of its branch offices. Those who are not members of the B.M.A. are required to pay nominal charges for the agency services.

THE BRITISH MEDICAL STUDENTS' ASSOCIATION

THIS association was founded in 1942 and its membership now includes over 90% of the medical students in the country. It is purely a professional organisation providing a means of communication between medical students in the different universities and hospitals and also between British students and those in other countries. It presents the medical students' viewpoint to the medical profession, to Government departments, and to other interested bodies. The organisation of the association is based on an annual general meeting at which an executive committee is elected, and on four regional councils. From time to time the association arranges clinical and preclinical conferences and "schools" which are appreciated not only for their academic interest but also for the opportunities which they provide for meeting fellow students from other medical schools. Local activities include lectures, visits, discussions, and the showing of films from the B.M.A. and other film libraries. Amongst its publications are the *British Medical Students' Journal*, which appears once a term, the B.M.S.A. Diary and an annual list of vacation appointments for those members requiring work in hospitals during vacations.

The B.M.S.A. is keenly interested in the grants problems of its members: cases of hardship are investigated and if necessary taken up with the appropriate authorities. In order to further this service a representative of the association sits as an observer on the National Union of Students grants and welfare committee.

The association has recently taken an active interest in the formation of the B.M.A.'s newly organised Junior Members Forum and its representatives attend the forum meetings. B.M.S.A. is represented on the other committees of the B.M.A. which discuss matters of interest to medical students and newly qualified doctors and on the undergraduate education committee of the College of General Practitioners. It also has liaison with the council of the College of General Practitioners. It maintains its close interest in the British Student Tuberculosis Foundation, of which it is a sponsoring body, and is a founder member of the United Kingdom committee of the World Health Organisation.

The association is a founder member of the International Federation of Medical Student Associations (I.F.M.S.A.), whose membership now embraces the associations of 21 nations, and the I.F.M.S.A. continues to develop successfully and is recognised by the World Medical Association and Unesco. Under the auspices of I.F.M.S.A. the annual Students' International Clinical Conference will be held this year in Scandinavia. This conference is one of the many opportunities available to members of the association, enabling them to travel and see something of medicine in other countries as well as meeting future doctors of many nationalities. Excellent arrangements also exist for foreign students to visit hospitals in this country and this year has seen an enormous increase in the number of students, both British and foreign, making use of these facilities. To encourage and assist deserving British students to attend courses and hospitals abroad the B.M.S.A. established four years ago a student travel fund. This year the administrators of the Fund awarded 24 scholarships to the total value of £200. It is hoped to improve further on this figure in future years. The B.M.S.A. is greatly indebted to the generous donors without whose gifts the international activities of the association would not be possible.

The principal interest of the association has continued to be the problem of the medical curriculum. Over the past two years the medical education subcommittee has prepared reports on entry to the medical course, the first year of medicine, and the preclinical curriculum. This year a detail survey of the clinical curriculum has been carried out, and it is hoped that the subcommittee's report will be available by the end of the year. This work has excited considerable interest amongst the profession and our views have been well received by a large number of medical educationalists. The subcommittee would be pleased to send reports to those interested and happy to receive comments on them.

The B.M.S.A. is fortunate to have a past president of the B.M.A., Sir Tudor Thomas, as its honorary president this year. The annual general meeting this year will be held in London on Nov. 12-14 and it is hoped that all member schools will send full delegations. Observers from the non-member schools will be very welcome.

The address of the association is B.M.A. House, Tavistock Square, London, W.C.1.

COMMONWEALTH MEDICAL ADVISORY BUREAU

THE British Medical Association set up the Commonwealth Medical Advisory Bureau with a view to making the stay of overseas medical visitors to this country as profitable and pleasant as possible, by welcoming them and providing a personal advisory service. The bureau, which is at B.M.A. House, Tavistock Square, London, W.C.1, caters for doctors from overseas parts of the Commonwealth who are staying in this country for postgraduate education or other purposes. Information is obtainable about postgraduate education and courses of study for higher qualifications, and inquirers can be put in touch with the organisations and authorities providing postgraduate education. The visitor who wishes to see something of the latest medical work in his own specialty can be put in touch with the appropriate experts.

A register of suitable hotels and lodgings is maintained by the bureau, and every effort is made to help visitors to solve the problem of finding somewhere to live. By social functions, and in other ways, overseas doctors are enabled to meet each other and prominent members of the profession in this country. General information about travel, sports facilities, exhibitions, theatres, &c., can also be given. The bureau can be of greatest service to the visitor if he writes as long as possible in advance of arrival, giving information on the following lines: projected date of arrival, mode of travel, whether accompanied by wife and children, period of stay, objects of the visit, and in what ways assistance is desired. If he wishes to visit hospitals or obtain advice on courses of study it is advisable for him to supply information about his own professional experience. On arrival a letter of introduction from the local hon. secretary of the visitors' medical association, although not essential, would be welcome. The medical director of the bureau is Dr. R. A. Pallister, to whom all communications should be addressed.

INTERNATIONAL MEDICAL ADVISORY BUREAU

THE British Medical Association has set up the International Medical Advisory Bureau to provide a personal advisory service to doctors visiting the United Kingdom from countries outside the British Commonwealth. The bureau, which is at B.M.A. House, Tavistock Square, London, W.C.1, offers information on postgraduate education facilities, visits to hospitals and clinics can be arranged, and help given in finding accommodation. General information on travel, car hire, theatres, and exhibitions is also available. The medical director is Dr. R. A. Pallister, to whom all communications should be addressed.

THE MEDICAL WOMEN'S FEDERATION

ALL medical women on the British Medical Register are eligible as members of the Medical Women's Federation, which has active local associations all over the country and in Northern Ireland, as well as a large London association and an overseas association linking up members all over the world. The federation is non-political. It provides medical and social meetings for its members and publishes a quarterly journal reviewing subjects of special interest to women doctors. These naturally cover a wide tract of social medicine, including maternity and child welfare, women in industry, the care of children and of difficult and delinquent children, the management of nursery schools and day-nurseries, women in prisons, children in approved schools and remand homes, the illegitimate child, and many related subjects. Advances in obstetrics and gynæcology, and psychological studies of women and children, are naturally of special interest to women doctors; recent work in these branches of medicine is reviewed in the journal. From time to time the federation undertakes social studies and publishes the results. It is also able to protect the interests of its members by presenting arguments in any cases where there has been discrimination against women doctors. The federation's headquarters are at Tavistock House North, Tavistock Square, London, W.C.1.

Notes and News

RES MEDICA

ONE of the newest medical journals comes from the oldest medical society in this country—the Royal Medical Society, formed at Edinburgh in 1737, only a few years after the medical faculty was founded in the university. Among royal societies this one is unique in that it is now run wholly by undergraduates, though its membership is not confined to students (or even to doctors), and it is unusual again in that it is not a university society, though it depends on the medical faculty for nearly all its members. Many men since famous have been its president—among them Sir Robert Hutchison, senior president in 1893, who contributed a foreword to the society's bicentenary history a few years ago.[1]

The society's new journal is called *Res Medica*.[2] Its contents will be derived mainly from the dissertations delivered by the student members on those Friday evenings in autumn and spring which "remain as always the society's highlight."

TWO OR THREE YEARS IN AUSTRALIA?

FOR at least a decade, people have been saying that there ought to be more exchange of young doctors between Commonwealth countries, and at one time, for example, there were hopes that hospitals in Britain and Australia would arrange to exchange residents for suitable periods. The scheme described by the State of Victoria in our advertisement columns this week is not an exchange scheme—though it originates perhaps from the fact that so many Australian graduates come to work for a time in this country. In proposing favourable terms on which men and women qualifying here can spend two or three years as residents in Australian country hospitals (ranging in size from about 100 to about 300 beds) the Government of Victoria are hoping, presumably, that a proportion will want to stay in their State, where the increase in the medical profession does not keep pace with the increase of population. For those who contemplate settling in Australia the scheme certainly offers an ideal introduction, but, even for those who fully intend to return, an Australian residency could be an unusually instructive and enlarging experience.

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[1] History of the Royal Medical Society 1737–1937. By JAMES GRAY. Edited by DOUGLAS GUTHRIE, F.R.C.S.E. Edinburgh, 1952.

[2] *Published from the society's headquarters, 7, Melbourne Place, Edinburgh, at 1s. per copy.*

A draft British standard for anæsthetists' trolleys (CI(M) 7456) (revision of B.S. 1938, part 2) has been issued by the British Standards Institution. Comments should reach the Institution, 2, Park Street, London, W.1, by Sept. 4.

Appointments

DAWSON, JOHN, M.B., M.SC. Leeds: director of biochemical research, Runwell Hospital, Essex.

GIBSON, A. C., M.B. Camb., M.R.C.P.E., D.P.M.: S.H.M.O., Runwell Hospital, Essex.

RENNIE, T. F., M.B. Aberd., D.P.H.: assistant M.O. and school M.O., Tiverton/Crediton area.

Colonial Appointments

- BROOKE, D. E., M.B. Lond.: M.O., Tanganyika.
- DEWAR, A. K., M.B. St. And.: M.O., Jamaica.
- FARQUHARSON, A. D. J., M.R.C.S., D.T.M. & H.: specialist (anæsthetist) curative services division, Northern Nigeria.
- HALL, C. L., B.M. Oxon., D.P.H.: A.D.M.S., Kenya.
- HUMPHREYS, G. S., M.B. Lond.: M.O., Trinidad.
- LEWIS, L. F. E., M.R.C.P.E., D.P.M.: superintending M.O. (specialist), Mental Hospital, Trinidad.
- MARTIN, J. A. M., M.B. Lond., D.L.O.: M.O., Uganda.
- READ, E. H. MCNEIL SMITH, M.D., M.R.C.P., D.C.H.: M.O. (pædiatrics), Jamaica.
- SANERKIN, N. G., M.D. Brist., M.R.C.P.E., D.C.P.: senior specialist (pathologist), *Cyprus*.
- SPENCER, JOHN, M.B. Lond.: M.O., Uganda.
- STROUD, C. E., M.B., B.SC. Wales, M.R.C.P., D.C.H.: M.O. (special grade), Uganda.
- WEBB, R. A. J., M.B. Lond.: assistant medical superintendent, Mental Hospital, Barbados.
- WOLF, JOSEPH, M.D. Bonn, M.B. N.U.I.: M.O., Brunei.

Births, Marriages, and Deaths

BIRTHS

FRYER.—On Aug. 19, at Aldershot, to June and David Fryer—a sister (Sarah Elizabeth) for Timothy, Hilary, and Martin.

The Lancet · Saturday 6 September 1958

THE PROPHYLAXIS OF IRON-DEFICIENCY ANÆMIA IN PREGNANCY

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IN the hundred and twenty years since Nasse wrote his original monograph on anæmia in pregnancy, a voluminous literature has appeared Some of the century-old controversies about the cause of this anæmia have been resolved with the advent of methods for measuring directly the plasma volume and red-cell mass It is now agreed that there are three main factors

(1) An increase in plasma volume that outstrips the simultaneous increase in red-cell mass (Dieckmann and Wegner 1934, Thomson et al 1938, Roscoe and Donaldson 1946, McLennan and Thouin 1948, Tysoe and Lowenstein 1950, Lund 1951, Berlin et al 1953)

(2) A deficiency of iron due to the demands of the fœtus (Rath et al 1950, Moore 1955, *Lancet* 1955)

(3) A deficiency of folic acid and possibly of cyanocobalamin due to the increased demands of the fœtus and of the pregnant woman and to impaired absorption during pregnancy

The megaloblastic anæmia of pregnancy accounts for only a very small proportion of cases of anæmia during pregnancy

The anæmias of pregnancy not due to folic-acid or cyanocobalamin deficiency have been divided by many authors into two groups—"hypochromic" and the so-called "physiological", the former being indistinguishable from iron-deficiency anæmia in non-pregnant women The "physiological" anæmia differs in certain important respects from iron-deficiency anæmia in non-pregnant women, as shown in table I, which was constructed after studying the published work of Dieckmann and Wegner (1934), Goodall and Gottlieb (1936), Fay et al (1949), Rath et al (1950), Hahn et al (1951), Caton et al (1951), Berlin et al (1953), and Verel et al (1956) Because of these dissimilarities, it has been argued that the "physiological" anæmia cannot be due to iron deficiency This view has been supported on the grounds that the red-cell mass often increases during pregnancy and returns to normal in the puerperium (Caton et al 1949, 1951, Berlin et al 1953) The argument, however, that has swayed medical opinion most cogently against the idea of a "physiological" anæmia of pregnancy has been the fact that it can usually be corrected with iron (Scott and Govan 1949, Klopper and Ventura 1951, Benstead and Theobald 1952, Davis and Jennison 1954, Lillie et al 1954, Fisher and Biggs 1955, Edgar and Rice 1956), which often causes a rise in mean corpuscular hæmoglobin concentration (M C H C) even when the latter was in the normal range before treatment The view that an anæmia which responds to iron in the same manner as a mild iron-deficiency anæmia cannot be physiological has recently gained wide acceptance, and many authorities now recommend that all women should receive iron supplements during pregnancy (*Lancet* 1955, 1956)

At the same time it should be noted that some workers (Fisher and Biggs 1955, Edgar and Rice 1956) have found that 10–20% of patients are anæmic in late pregnancy even when adequate doses of iron have been prescribed Several possible explanations have been suggested (1) failure to take the prescribed iron, (2) failure to absorb iron, (3) mild folic-acid deficiency, (4) an unusually large increase in plasma volume Since the last is probably the most important factor, a simple, safe and satisfactory procedure for the measurement of red-cell mass which did not involve the use of radioactive isotopes would be very helpful in determining the nature of these refractory cases

The incidence of anæmia varies considerably in different populations, according to the economic conditions (Strauss and Castle 1932, Davidson et al 1935, Fullerton 1936, Doyle and McGrath 1954), and considerable social changes have taken place in Edinburgh since the last survey (Roscoe and Donaldson 1946) To help formulate a practical policy for the prophylaxis of iron-deficiency anæmia in pregnancy we have therefore undertaken a study on patients attending the Simpson Memorial Maternity Pavilion, Edinburgh, to ascertain

(1) The incidence of anæmia in pregnancy

(2) The effect of season, age, parity, recent pregnancy, and duration of pregnancy on the incidence and degree of anæmia

(3) The adequacy of the present diet of Edinburgh mothers

(4) The most suitable forms of oral iron to administer, if supplements are necessary, in regard to their efficiency, economy, and lack of undesirable side-effects

(5) The stage in pregnancy at which iron supplements should be started

(6) Whether the addition of ascorbic acid to ferrous gluconate pills confers any advantage upon them

The effect of adding ascorbic acid to the iron pills was investigated because (*a*) ascorbic acid aids the absorption of iron (Powell 1944, Moore 1955), (*b*) a deficiency of ascorbic acid increases the incidence of anæmia in pregnancy, and the administration of ascorbic acid corrects the anæmia, though less effectively than iron (Scott and Govan 1949), and (*c*) tablets containing ascorbic acid as well as iron are stated to be better tolerated than iron alone (Fisher and Biggs 1955)

Investigation of Incidence of Anæmia

To obtain information in regard to problems 1 and 2 a study was made of the case-notes of all the patients attending the antenatal clinic of the Simpson Memorial Maternity Pavilion, in the periods February–March and August–September of 1955 and 1956 After excluding patients who were found to have any disease likely to

TABLE I—COMPARISON OF IRON-DEFICIENCY ANÆMIA WITH "PHYSIOLOGICAL" ANÆMIA OF PREGNANCY

—	Iron-deficiency anæmia	"Physiological" anæmia of pregnancy
Colour index	Low	Normal
M C.H C.	Low	Low normal
M C V	Low	High normal
Reticulocyte count	Low	Raised
Serum iron	Low	Normal or low
Iron-binding capacity (I.B C.)	High	High
Ratio of serum iron to I B.C.	Very low	Low
Iron absorption	Increased	Increased
Free erythrocyte protoporphyrin	Increased	Slightly increased
Serum copper	High	High
Total red cell mass	Low	Normal or increased
Total body hæmoglobin	Low	Normal or increased
Plasma volume	Increased +	Increased +++
Response to iron therapy	Rise in Hb +++	Rise in Hb +

cause anæmia or who were receiving iron at the time of their first visit, the number of case-notes available for analysis was 1994—an average of about 500 patients for each of the four periods Hæmoglobin levels were estimated routinely at the first visit by the oxyhæmoglobin method, in an EEL photoelectric colorimeter, using capillary blood obtained by pricking the finger

Of these 1994 patients, 1071 attended the clinic for the first time before the twelfth week of pregnancy (table II) Of this number *631* required and received iron medication, the remaining 440 patients were given no iron Table VII summarises the changes in hæmoglobin level in these 440 women between the first visit and the 23rd to 27th week of pregnancy

Tables II–VI show the incidence of anæmia in the 1994 patients in relation to the stage of pregnancy at their first visit, the season when they were first seen at the clinic, their age, their parity, and the number of their pregnancies within the previous five years

FINDINGS

Incidence of anæmia (table II)—The mean hæmoglobin level of 1071 women seen initially in the first 11 weeks of pregnancy, a period during which the occurrence of hydræmia is insignificant, was 12 9 g per 100 ml (88%) (Hæmoglobin percentages given are based on the scale that 14 8 g per 100 ml = 100%) A hæmoglobin level below 10 4 g (70%) was found in 2% of the women, while 32% had a level below 12 6 g (85%)

TABLE II—HÆMOGLOBIN LEVEL AT FIRST ANTENATAL VISIT IN 1955–56

Week in pregnancy when Hb level was estimated	No of patients	Mean hæmoglobin level		Standard deviation	
		g per 100 ml	%	g per 100 ml	%
1–40	1994	12 6	85	1 30	8 8
1–11	1071	13 0	88	1 39	9 4
12–23	698	12 4	84	1 31	8 9
24–40	225	11 6	78	1 32	8 9

The mean hæmoglobin level was lower in women first seen at a later stage in pregnancy, the difference being highly significant ($P<0\ 001$) Of the 225 women first seen at the 24th week or later, 13 7% had a hæmoglobin level of less than 10 4 g per 100 ml (70%) and 78 1% had a hæmoglobin level of less than 12 6 g per 100 ml (85%)

Seasonal variation (table III)—Women first seen at the end of the winter (i e, in February and March) had higher hæmoglobin levels on the average than those first seen at the end of the summer (i e, in August and September) The difference between these two groups is highly significant ($P<0\ 001$)

Effect of age (table IV)—To assess the effect of age on the incidence of anæmia, without the complicating factors of previous pregnancies and iron therapy, the case-records of 300 primigravidæ seen in 1955 who were not receiving iron therapy at the time of examination were analysed No significant difference was found between the mean initial hæmoglobin levels of women under and over 25 years of age Subdivision into narrower age-groups again showed no significant difference Age has therefore been ignored in assessing the effect of parity

Effect of parity (table V)—The mean hæmoglobin levels of 618 primigravidæ and 390 parous women were compared at different stages of pregnancy No significant difference was found ($P>0\ 3$)

TABLE III—SEASONAL VARIATION IN THE INCIDENCE OF ANÆMIA I PREGNANCY COMPARISON BETWEEN WOMEN WHO FIRST ATTENDED TH ANTENATAL CLINIC AT THE END OF THE SUMMER (AUGUST–SEPTEMB AND AT THE END OF WINTER (FEBRUARY–MARCH) 1955 AND 1956

Stage in pregnancy when Hb level was estimated (weeks)	Season	No of patients	Mean hæmoglobin level		Standard deviation	
			g per 100 ml	%	g per 100 ml	%
0–11	Summer	534	12 5	84	1 11	75
	Winter	537	13 5	91	1 26	85
12–23	Summer	358	12·0	81	1 11	7·5
	Winter	340	12 8	87	1 36	92
24–40	Summer	99	11 1	75	1 23	83
	Winter	126	11 8	80	1 30	88

Effect of recent pregnancies (table VI)—The me hæmoglobin levels of women who had borne no childre one child, or two *or more* children *within the five ye* period preceding the present pregnancy were compare There was no significant difference between the groups

Fall in hæmoglobin level during second trimester—The mean fall in hæmoglobin level between the fir estimation (during first 11 weeks of pregnancy) an second estimation (23rd–27th week of pregnancy) in th 440 women who were known to have received no iron *shown in table* VII, *where it is compared with the* init hæmoglobin level The fall was greatest in those wome with an initially high hæmoglobin level, even when was expressed as a percentage of the original lev The difference in the mean fall in hæmoglobin level patients with an initial hæmoglobin level of 12 6 g p 100 ml (85%) or more was significantly greater ($P<0\ 0$ than in those patients with an initial hæmoglobin lev *below 12 6 g*

Investigation of Iron Preparations

To obtain information about the potency and toxici of certain iron preparations an investigation was unde taken of all women attending the antenatal clinic of th Simpson Memorial Maternity Pavilion between Marc *1956*, and *June, 1957*, during their *24th* or 25th week pregnancy, provided that

(1) Their hæmoglobin level was 10 4 g per 100 ml o above

(2) They had no disease likely to cause anæmia or excessiv hydræmia

(3) They did not have twins

(4) They were not already receiving iron therapy

(5) They intended to continue attending the antenatal clin till term

The 430 women accepted for this investigation wer assigned by random selection (choosing a card from pack) to one of four groups Group A (20%) receive ferrous sulphate, group B (20%) received ferrou gluconate, group C (20%) received ferrous gluconat plus ascorbic acid, and group D (40%) formed th control group which received pills containing lactose

The pills prescribed were identical in shape, colour, an

TABLE IV—EFFECT OF AGE ON THE LEVEL OF HÆMOGLOBIN OF 3 PRIMIGRAVIDÆ

Stage in pregnancy when Hb level was estimated (weeks)	Age	No	Mean hæmoglobin level		Standard deviation	
			g per 100 ml	%	g per 100 ml	%
0–11	Under 25	97	12 9	87	0 83	5·6
	25 and over	90	12·9	87	1 03	7·0
12–23	Under 25	81	12 2	83	0·99	6 7
	25 and over	32	12·0	81	1·04	7·0

TABLE V—EFFECT OF PARITY ON THE HÆMOGLOBIN LEVEL OF 618 PRIMIGRAVIDÆ AND 390 PAROUS WOMEN

Stage in pregnancy when Hb level was estimated (weeks)		Season	No of patients	Mean hæmoglobin level		Standard deviation	
				g per 100 ml.	%	g per 100 ml	%
1–11	Prim.	Summer	184	12·3	83	1·02	6·9
	Parous.	Summer	81	12·3	83	1·05	7·1
	Prim.	Winter	181	13·0	88	1·20	8·1
	Parous	Winter	94	13·2	89	1·11	7·5
12–23	Prim	Summer	97	11·8	80	1·12	7·6
	Parous	Summer	71	11·9	81	1·07	7·2
	Prim	Winter	103	12·4	84	1·26	8·5
	Parous.	Winter	65	12·4	84	1·38	9·3
24–40	Prim.	Summer	21	11·2	76	1·27	8·6
	Parous	Summer	33	11·1	75	1·05	7·1
	Prim	Winter	32	11·5	78	1·26	8·5
	Parous	Winter	36	11·6	78	1·01	6·8

coating As the control group was larger than the others, it was necessary for the doctors conducting the trial to know which were the control pills, the other three preparations were known as pills A, B, and C, and their identity was not known to patients or doctors until the trial was finished and the results had been analysed.

Careful consideration was given to the dosage of iron to be incorporated in the pills It was essential that the daily iron intake should be the same irrespective of which preparation was being taken. The dose of ferrous gluconate usually recommended is one 300 mg (gr 5) pill containing 35 mg of elemental iron, given three times a day, making a total of 105 mg of iron daily Ferrous sulphate, however, is usually prescribed as one 180 mg (gr 3) pill containing 60 mg of elemental iron, three times a day, making a total of 180 mg of iron daily We had to decide at the outset whether to increase the dose of elemental iron in each ferrous-gluconate pill to 60 mg—i e, approximately double the usual therapeutic dose—or to reduce the amount of elemental iron in each ferrous-sulphate tablet from 60 mg to 35 mg The latter choice was made because we wished to know not only about the therapeutic efficiency of ferrous gluconate and the incidence of side-effects when it was given in the usual dosage mentioned above, but also whether the addition of 25 mg of ascorbic acid to each ferrous-gluconate pill would increase its efficiency or reduce its toxicity Accordingly each ferrous-sulphate and ferrous-gluconate pill used in this investigation contained 35 mg of elemental iron.

Each patient was given both oral and written instructions which explained that she was going to be given a preparation of iron to prevent or cure the anæmia which tended to develop in pregnancy It was also emphasised that the pills were to be taken three times a day after food, and stress was placed on the need to take them regularly for the period prescribed No mention was made of control pills containing lactose The possibility that 40% of pills ingested did not contain iron was apparently not suspected by the patients, since only 2 commented on the fact that their motions were not black

Patients were recalled for the second interview at the 37th week, when each was asked to estimate her weekly intake of certain iron-containing foods (meat, liver, bacon, fish, eggs, soups, potatoes, cereals, bread, milk, beverages, chocolate) during the period of the trial From this her daily intake of iron was calculated, figures for the iron content of foods were taken from tables constructed by McCance and Widdowson (1946)

At this second interview patients were asked whether they had suffered any symptoms from taking the pills, and if so whether they interfered with the treatment. Symptoms were graded "mild" (no interference with treatment) "moderate" (temporary interruption of treatment) and "severe" (obliged to stop treatment) Only gastrointestinal symptoms were recorded as being due to the pills Patients were also asked whether they had taken the pills conscientiously Only 6 of the patients who did not complain of intolerance to iron admitted that they had taken the pills irregularly

37 women were unable to take the prescribed course of pills because of "severe" toxic effects In addition 61 failed to complete the trial because of premature delivery, conditions complicating pregnancy (e g, toxæmia), intercurrent illness, removal from the district, or unwillingness to cooperate

Hence of the original 430 patients, 332 took their pills regularly and came to the second interview A study has been made of the potency of the different oral iron preparations used in the treatment of this group of women The 61 women who failed to attend were sent a questionnaire in which they were asked to record any gastrointestinal symptoms experienced while taking the pills From these questionnaires and from the information given by the 369 women (332 + 37) attending the second interview, it was possible to analyse the incidence of toxic symptoms in a total of 410 patients

TABLE VI—EFFECT ON HÆMOGLOBIN LEVEL OF NUMBER OF PREGNANCIES WITHIN THE LAST FIVE YEARS (PATIENTS SEEN IN 1955)

Stage in pregnancy when Hb level was first estimated (weeks)	Season	Pregnancies within last five years	No in group	Mean hæmoglobin level		Standard deviation	
				g per 100 ml	%	g per 100 ml	%
0–11	Summer	0	202	12·8	87	1·08	7·3
		1	56	12·4	84	1·29	8·7
		2 or more	11	12·1	82	1·15	7·8
	Winter	0	173	13·8	93	1·21	8·2
		1	75	14·1	96	1·29	8·7
		2 or more	15	14·4	97	1·45	9·8
12–23	Summer	0	120	12·1	82	1·10	7·4
		1	48	12·2	82	1·18	8·0
		2 or more	23	12·0	81	1·11	7·5
	Winter	0	106	13·2	89	1·29	8·7
		1	42	13·3	90	1·55	10·5
		2 or more	24	12·8	87	1·27	8·6

Venous blood was taken, with minimum stasis, at the 24–25th week and at the 37th week, and the hæmoglobin level (Hb), red-cell count (R.B C), and packed-cell volume (P C.V) measured

Hæmoglobin was estimated by the alkaline hæmatin method, using an E E L photoelectric colorimeter, red-cell counts were performed in duplicate in Neubauer counting-chambers, packed-cell volumes were measured after centrifugation for thirty minutes at 3000 r p.m in a standard hæmatocrit centrifuge. Between the two blood-tests the patients were not

TABLE VII—FALL IN HÆMOGLOBIN LEVEL DURING SECOND TRIMESTER IN 440 PATIENTS NOT RECEIVING IRON THERAPY

Initial hæmoglobin range		No of patients	Mean fall in hæmoglobin level		Standard deviation		Mean fall in hæmoglobin level as % of initial hæmoglobin level
g per 100 ml.	%		g per 100 ml.	%	g per 100 ml	%	
10·4–10·9	70–74	5	0·7	5	0·36	2·4	6·4
11·1–11·7	75–79	25	1·2	8	0·70	4·7	10·3
11·8–12·4	80–84	79	1·5	10	0·77	5·2	12·7
12·6–13·2	85–89	133	1·7	12	0·76	5·1	12·9
13·3–13·9	90–94	102	2·1	14	0·80	5·4	15·5
14·1–14·6	95–99	66	2·5	17	0·84	5·7	17·2
14·8–15·4	100–104	30	3·0	20	1·60	10·8	19·6

TABLE VIII—CHANGE IN HÆMOGLOBIN LEVEL, RED-CELL COUNT, AND PACKED-CELL VOLUME BETWEEN 24–25TH AND 37TH WEEK O PREGNANCY IN THE FOUR TREATMENT GROUPS

Hæmoglobin Levels

Treatment	No in group	Initial mean Hb level		Mean change in Hb level		Standard deviation	
		g per 100 ml	%	g per 100 ml	%	g per 100 ml	%
Ferrous sulphate	67	12·0	81	+0·7	+5	1·12	7·6
„ gluconate	67	12·0	81	+1·1	+7	1·18	8·0
„ „ plus ascorbic acid	70	11·9	80	+1·0	+7	0·90	6·1
„ „ (total)	137	12·0	81	+1·1	+7	1·06	7·2
Control	128	12·1	82	−0·4	−3	1·15	7·8

Red-cell Count

Treatment	No in group	Initial mean R B C (million per c mm)	Mean change in R B C (million per c mm)	Standard deviation (million per c mm)
Ferrous sulphate	67	3·9	+0·3	0·30
„ gluconate	67	3·9	+0·4	0·40
„ „ plus ascorbic acid	70	3·9	+0·4	0·35
„ „ (total)	137	3·9	+0·4	0·37
Control	128	3·9	+0·0	0·36

Packed-cell Volume

Treatment	No in group	Initial mean P C V (%)	Mean change in P C V (%)	Standard deviation (%)
Ferrous sulphate	67	36·4	+2·7	2·3
„ gluconate	67	36·1	+3·2	2·7
„ „ plus ascorbic acid	70	36·0	+2·7	2·3
„ „ (total)	137	36·0	+2·9	2·2
Control	128	36·3	−0·6	1·9

normally seen by the investigators, but were supervised by the obstetricians. This supervision included further routine hæmoglobin estimations—usually two. Any patient whose hæmoglobin fell below 10·4 g. per 100 ml. (70%) was referred to the investigators. 11 patients taking control tablets were seen on this account; they were excluded from the trial and given iron pills. All responded normally. 4 who were taking iron pills were referred for the same reason. Additional counts were carried out. 1 patient was found to have megaloblastic anæmia of pregnancy; the remaining 3 were left on the same treatment, and eventually responded with a rise in hæmoglobin level.

FINDINGS

Dietary survey.—The replies by 95 successive patients taking control pills, who answered a more detailed dietary questionnaire, were analysed. The mean dietary intake of iron was estimated at about 11 mg. This was not the total intake, for only the major iron-containing foods were included in the questionnaire, but it was thought to represent 80–90% of the intake for the average woman. This gave an estimated mean iron consumption of approximately 13 mg. daily—an intake slightly below the minimum level of 15 mg. recommended for pregnant women by the B.M.A. Sub-Committee on Nutrition in 1950.

Effect of diet on hæmoglobin level.—The fall in hæmoglobin level in the 95 women in the control group during the last trimester of pregnancy has been compared with their estimated dietary intake of iron. The mean fall in 26 patients whose diet was unsatisfactory as regards iron (i.e., reckoned to contain less than 10 mg. daily) was 0·6 g. per 100 ml. (4%), whereas the mean fall in 69 patients whose dietary intake of iron was reckoned to be more than 10 mg. (16 of whom ingested more than 14 mg. daily) was 0·4 g. per 100 ml. (2·7%). It is obvious therefore that factors other than the total content of iron in the diet were important in determining the final hæmoglobin level. It is of interest that some women reckoned to be taking more than the recommended intake of 15 mg. of iron a day were found to have a considerable fall in hæmoglobin level.

Comparison of the iron preparations.—The changes in hæmoglobin level, red-cell count, and packed-cell volume in the four treatment groups are shown in table VIII. Hæmoglobin levels and packed-cell volume rose in each of the iron-treated groups and fell in the control group, the difference being significant (P<0·01). The red-cell count rose slightly in the control group, but the rise in each treatment group was significantly greater (P<0·05). These differences between the control and treatment groups would have been larger had not 11 patients who were originally assigned to the control group been excluded from the trial because their hæmoglobin level fell below 10·4 g. per 100 ml. (70%).

No significant difference between the changes in hæmoglobin level, red-cell count, and packed-cell volume was observed in the two groups treated with ferrous gluconate, with and without ascorbic acid (P>0·3). We conclude, therefore, that the addition of ascorbic acid does not affect the therapeutic value of ferrous gluconate, either beneficially or adversely. Accordingly the two groups treated with ferrous gluconate have been amalgamated and compared with the group treated with ferrous sulphate. The rise in hæmoglobin level, red-cell count, and packed-cell volume in the ferrous-sulphate group is less than in the groups receiving ferrous gluconate; the difference is significant (0·01<P<0·05) for the red-cell count, barely significant (P = 0·05) for the hæmoglobin level, and not significant (P<0·05) for the packed-cell volume.

The incidence of gastrointestinal intolerance to the pills is shown in table IX. There is no significant difference

TABLE IX—INCIDENCE OF GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS

Iron preparation	No in group	Percentage showing symptoms			
		Nil	Mild	Moderate	Severe
Ferrous sulphate	81	75	11	7	6
„ gluconate	88	66	16	8	10
„ „ plus vitamin C	82	72	10	6	12
Control (lactose)	159	74	13	4	9

TABLE X—FALL IN HÆMOGLOBIN LEVEL AND PACKED CELL VOLUME DURING THIRD TRIMESTER IN PATIENTS NOT RECEIVING IRON THERAPY

Initial Hb level		No of patients	Hb level				P.C.V.	
			Mean change		Standard deviation		Mean change (%)	Standard deviation (%)
g per 100 ml	%		g per 100 ml	%	g per 100 ml	%		
10·36–11·69	70–79	43	−0·10	−0·7	0·95	6·4	−0·2	3·9
11·84 and over	80	85	−0·62	−4·2	1·15	7·8	−0·8	3·3

between the control pills and the iron pills, or between the three iron preparations. This suggests that most of the symptoms attributed by the patients to iron medication were either incidental or psychogenic in origin. It was thought possible that the gastrointestinal symptoms (morning sickness, heartburn, constipation) which are liable to occur in pregnancy might be obscuring the incidence of symptoms due to iron intolerance. An investigation of the side-effects of oral iron medication was therefore carried out on 93 normal women who were not pregnant. The results (Kerr and Davidson 1958) are very similar to those in the pregnant women and clearly demonstrate the great *importance of the psychological factor*.

Discussion

Although severe anæmia is now uncommon in pregnant women in Edinburgh, the incidence of mild anæmia at the beginning of pregnancy is still sufficient to justify wide-scale prophylaxis with oral iron therapy. Like many other authors, we noted a fall in the hæmoglobin level in the later stages of pregnancy.

The seasonal variation in the incidence is interesting.

Our findings that the incidence is highest at the end of summer contrasts with the finding of some other workers (Scott and Govan 1949, Lund and Kimble 1943, Doyle and McGrath 1954, Gatenby and Lillie 1955) who described a lower incidence in summer. We must frankly admit that we know of no satisfactory explanation of the seasonal fluctuations in the hæmoglobin level. They might reflect changes in the diet, but in our survey these were so small that they could have had no effect on the amount of iron in the food. Although no information was collected regarding the intake of fruit and vegetables, there are several reasons which convince us that the seasonal changes in the incidence of anæmia shown in table III are unlikely to be due to seasonal variations in the intake of iron and ascorbic acid derived from these sources.

No increase in susceptibility to anæmia was found with increasing age; this contrasts with the finding of Roscoe and Donaldson (1946), but these workers compared all women regardless of parity, whereas we compared primigravidæ only. Anæmia did not increase significantly with the number of children, or with the number of pregnancies in the previous five years. This is in marked contrast to the experience of one of us (S. D.) twenty-five years ago in Aberdeen. The most likely causes of the change are (1) the great improvement in the social and economic status of the working classes, particularly in the past fifteen years, (2) the stress laid by teachers of medicine on the importance of menstruation and pregnancy in the ætiology of iron-deficiency anæmia, and (3) routine hæmoglobin estimations in antenatal clinics and maternity hospitals and the administration of iron to all patients who are found to need it.

The fall in hæmoglobin level during the second and third trimesters, noted by previous workers was found in women who were not given iron. It is of interest that the women with initially high hæmoglobin levels sustained the biggest fall in hæmoglobin during the second trimester, and this was true also, though in lesser degree, during the third trimester (table X). The explanation is uncertain: possibly iron is absorbed more avidly in early pregnancy by patients who are already anæmic. Whatever the cause, the observation is of some practical importance because it means that a normal hæmoglobin level at the beginning of pregnancy, or even at the 24th week, does not guarantee the patient against anæmia at term. From the data used in compiling tables VII and X we were able to calculate that a woman (in the population studied) with an initial hæmoglobin range of 12·5 to 15·0 g. per 100 ml. (84–101%) at the beginning of pregnancy stands roughly a 10% chance of reaching "term" with a hæmoglobin level of less than 10 g. per 100 ml. (68%) if she is given no iron during pregnancy.

Administration of 105 mg. of iron daily between the 24th and 37th weeks caused a mean rise in hæmoglobin level, red-cell count, and packed-cell volume. This is a relatively small dose of iron and the final mean hæmoglobin level achieved—13·0 g. per 100 ml. (88%)—is not as high as that recorded by some other workers who used larger doses of iron, or the same dose for longer periods (Benstead and Theobald 1952, Edgar and Rice 1956). However, it is to be expected that the hæmoglobin level will rise further between the 37th week and term, as it rises slightly at this stage in pregnancy even in untreated patients, we feel that a final mean hæmoglobin level of about 13·5 g. (91%) at term is reasonably satisfactory. There are several reasons for giving iron routinely in late rather than early pregnancy. Firstly it has been shown that iron is better absorbed at this stage (Hahn et al. 1951). Secondly there is a considerable saving of money and trouble to the patient by limiting iron therapy to the last trimester. Thirdly the fœtal demands for iron are at their maximum. And fourthly therapeutic results will generally be found to be satisfactory.

Like Fisher and Biggs (1955) and Edgar and Rice (1956), we found that a proportion of the patients treated with iron failed to show a rise in hæmoglobin level (24% of those on ferrous sulphate and 23% of those on ferrous gluconate).

As a result of our investigations we suggest the following scheme of supervision for antenatal patients:

(1) Routine hæmoglobin estimation at the first antenatal visit. This has been the practice for many years in the Simpson Memorial Maternity Pavilion.

(2) Iron therapy from the first visit for all patients with an initial hæmoglobin level of less than 12·6 g. per 100 ml. (85%).

(3) Routine administration of elemental iron in a dosage of at least 105 mg. daily to all patients from the 24th week to term. This dosage is provided by one 300 mg. (gr. 5) pill of *ferrous gluconate*, three times a day. The customary dose of ferrous sulphate is one 180 mg. (gr. 3) pill three times a day which provides a much greater amount of elemental iron, namely 180 mg. per day.

The choice of preparation for iron therapy remains controversial This study suggests that ferrous gluconate may be slightly more efficient than ferrous sulphate (when given in the same dosage in terms of elemental iron—namely, 105 mg daily) in raising the hæmoglobin level, but the difference is barely significant Lillie et al (1954) claim that ferrous gluconate is slightly superior to ferrous sulphate in restoring the hæmoglobin level of anæmic persons, even when the amount of iron in the dose of ferrous sulphate given was greater However, the level *of significance is not stated and their two groups of* patients were not selected at random or concurrently In contrast O'Sullivan et al (1955) in a very carefully controlled investigation into the treatment of iron-deficiency anæmia in non-pregnant patients could find no significant difference in therapeutic efficacy between ferrous gluconate, ferrous succinate, and ferrous sulphate, all three preparations being given in a daily dose of 210 mg of elemental iron It seems to us, therefore, only reasonable to believe that better results would be obtained from giving 180 mg of iron daily in the form of ferrous sulphate than from giving ferrous gluconate in a daily dose containing 105 mg of iron, in which case the choice of preparation will depend essentially on relative cost and the frequency and severity of undesirable side-effects

From our inquiries in Edinburgh we are satisfied that ferrous sulphate is the least expensive preparation of iron available (Davidson and Richmond 1958)

As already noted, we have not been able to demonstrate any difference in the incidence of gastrointestinal intolerance between women receiving ferrous sulphate and those receiving ferrous gluconate—105 mg of iron daily in each case In fact, the incidence was the same in those taking the control lactose pills We attach great importance to the psychological factor in iron intolerance, and our experience is that the great majority of persons, pregnant or non-pregnant, can take one gr 3 ferrous-sulphate tablet thrice daily without experiencing any significant side-effects, provided the tablet is always taken after meals and the patient is assured by her doctor that the pills will cause no discomfort

We have not demonstrated that the addition of ascorbic acid to ferrous gluconate increases its therapeutic efficiency or reduces its side-effects This conclusion does not necessarily apply to populations whose diet contains less ascorbic acid, but in Britain today the use of iron-plus-ascorbic-acid pills appears to be a needless expense

Summary

(1) The incidence of anæmia in pregnancy in Edinburgh in 1955 and 1956 has been estimated Although severe anæmia is rare at the beginning of pregnancy, mild anæmia ($Hb < 12 6$ g per 100 ml [85%]) is common

(2) No correlation has been found between the incidence of anæmia and age, parity, or the number of pregnancies within the previous five years Possible reasons for these findings are discussed

(3) An estimate of the average daily dietary intake of iron in pregnant women in Edinburgh suggests that it is slightly less than the 15 mg usually recommended The incidence or degree of anæmia was not found to correspond closely with the dietary intake of iron

(4) Oral administration of iron supplements during the third trimester corrects the anæmia of pregnancy in about 80% of cases, even when the initial mean corpuscular hæmoglobin content is normal This time of administration appears to be suitable for routine purposes

(5) As regards gastrointestinal side-effects, no difference was found between ferrous sulphate and ferrous gluconate, given in doses containing 105 mg of iron daily Neither preparation caused significantly more unpleasant gastro-intestinal symptoms than the other or than the control pills containing lactose

(6) The addition of ascorbic acid to ferrous-gluconate pills has not been shown to increase their therapeutic efficacy or to reduce their toxic effects

We wish to express our gratitude to Prof R J Kellar and D Douglas Miller for permission to carry out this study at their clinics, and for their encouragement and help, to Dr F J Scandrett of th clinical research laboratories of the Simpson Memorial Maternity Pavilion, Edinburgh, whose staff was responsible for the routine blood examinations analysed in our investigation of the incidence of anæmia, to Sister Mary Stirling, sister-in-charge of the antenatal clinic, and to Dr J Richmond, Dr A Doig, and Dr E J Watson-Williams, and to Mr R Samson, technician, of the staff of the University department of medicine, who assisted in the investigation of iron preparations We are also indebted to Messrs John Wyeth and Brother Limited for the iron preparations tested and fo financial assistance, and to Dr Gordon Fryers, medical director, for his advice and help

REFERENCES

Benstead, N , Theobald, G W (1952) *Brit med J* i, 407
Berlin, N I , Goetsch, G , Hyde, G M , Parsons, R J (1953) *Surg Gyn Obstet* 97, 173
Caton, W L , Roby, C C , Reid, D E , Gibson, J G (1949) *Amer J Obstet Gynec* 57, 471
— — — Caswell, R , Maletskos, C J , Fluharty, R G , Gibson, J G (1951) *ibid* 61, 1207
Davidson, L S P , Fullerton, H W , Campbell, R M (1935) *Brit med J* ii, 195
— Richmond, J (1958) *Lancet*, (in the press)
Davis, L R , Jennison, R F (1954) *J Obstet Gynec Brit Emp* 61, 103
Dieckmann, W J , Wegner, C R (1934) *Arch intern Med* 53, 71, 345
Doyle, G D , McGrath, J (1954) *Irish J med Sci* 6th ser , p 414
Edgar, W , Rice, H M (1956) *Lancet*, i, 599
Fay, J , Cartwright, G E , Wintrobe, M M (1949) *J clin Invest* 28, 487
Fisher, M , Biggs, R (1955) *Brit med J* i, 385
Fullerton, H W (1936) *ibid* ii, 523, 577
Gatenby, P B B , Lillie, E W (1955) *Lancet*, i, 740
Goodall, J R , Gottlieb, R (1936) *Canad med Assoc J* 35, 50
Hahn, P F , Carothers, E L , Darby, W J , Martin, M , Sheppard, C W , Cannon, R O , Beam, A S , Densen, P M , Peterson, J C , McClellan, G S (1951) *Amer J Obstet Gynec* 61, 477
Kerr, D N S , Davidson, L S P (1958) *Lancet*, ii, 489
Klopper, A , Ventura, S (1951) *Brit med J* ii, 1251
Lancet (1955) i, 655
Lancet (1956) i, 843
Lillie, E W , Gatenby, P B B , Moore, H C (1954) *Irish J med Sci* 6th ser p 304
Lund, C J (1951) *Amer J Obstet Gynec* 62, 947
— Kimble, M S (1943) *ibid* 46, 635
McLennan, C E , Thouin, L G (1948) *ibid* 55, 189
McCance, R A , Widdowson, E M (1946) *Spec Rep Ser med Res Coun, Lond* no 235
Moore, C V (1955) *Amer J clin Nutr* 3, 3
Nasse, H (1836) Das Blut in mehrfacher Beziehung physiologisch und pathologisch untersucht Bonn
O Sullivan, D J , Higgins, P G , Wilkinson, J F (1955) *Lancet*, ii, 482
Powell, J F (1944) *Quart J Med* n s 13, 19
Rath, C E , Caton, W , Reid, D E , Finch, C A , Conroy, L (1950) *Surg Gynec Obstet* 90, 320
Roscoe, M H , Donaldson, G M M (1946) *J. Obstet Gynæc Brit Emp* 53, 430, 527
Scott, J M , Govan, A D T (1949) *Brit med J* ii 1083
Strauss, M B , Castle, W B (1932) *Amer J med Sci* 184, 663
Thomson, K J , Hirsheimer, A , Gibson, J G , Evans, W A (1938) *Amer J Obstet Gynec* 36, 48
Tysoe, P W , Lowenstein, L (1950) *ibid* 60 1187
Verel, D , Bury, J D , Hope, A (1956) *Clin Sci* 15, 1

"The need for accuracy, orderliness and a strict observance of rules increases in proportion as clinical and surgical techniques become more complex, more scientific, more a matter of the co-ordinated and carefully timed activity of a medical and nursing team Moreover, many of the new therapeutic and diagnostic procedures are, not infrequently, a serious threat to the patient's life As the risk increases so does the need for accuracy and order Thus, the system of rules and regulations which governs the performance of duties and the hierarchical relationships between different medical and nursing groups tends to become more complex and rigid"—RICHARD M TITMUSS, *Essays on "The Welfare State"*, p 201 London, 1958

GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS

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IT was the opinion of Thomas Sydenham that "iron may be given in the largest doses without inconvenience" His optimistic view has been shared in later generations by the originators of a large number of oral iron preparations which now compete for favour in the advertisement columns of the medical press There is, however, a widespread belief among patients that iron inevitably causes gastrointestinal disturbance, particularly constipation

To most patients ten years ago "iron" was synonymous with green ferrous-sulphate tablets This preparation's popularity with the medical profession was well deserved In correcting iron-deficiency anæmia it had been found at least as effective as any of the other available preparations (ferrous chloride, ferrous carbonate, iron and ammonium citrate, colloidal iron) and it had a considerable advantage in cost and convenience (Davidson and Fullerton 1938) During the past ten years a number of organic iron preparations have appeared on the market, and have been widely used It is therefore desirable to re-examine the question of which oral preparation of iron is the most suitable for the treatment of anæmia, in both pregnant and non-pregnant patients

O'Sullivan et al (1955) compared three of the most popular preparations—ferrous sulphate, ferrous gluconate, and ferrous succinate They gave the three compounds, in doses containing equal amounts of elemental iron (210 mg daily) to matched groups of patients, and found similar rises in hæmoglobin level Few other comparisons between iron compounds have been made with the same control of dosage and type of patient, but numerous papers attest the therapeutic effectiveness of most of the popular iron pills Ferrous sulphate (Benstead and Theobald 1952, Devoe and Moses 1954, Talaga 1955, Gatenby and Lillie 1955, O'Sullivan et al 1955), ferrous gluconate (Jasinski 1949, Haler 1952, Gatenby and Lillie 1955, O'Sullivan et al 1955), ferrous succinate (O'Sullivan et al 1955, Gillhespy 1955, Cope et al 1956, Storm Mathiesen and Petersen 1956), ferrous calcium citrate (Talaga 1955), and several other compounds (Davidson and Fullerton 1938) have been shown to be capable of correcting iron-deficiency anæmia In most of the papers cited, a rise in hæmoglobin level of more than 1% per day was obtained when the pills were taken conscientiously in the recommended dosage Since the published evidence does not show that any one of these compounds is more efficient than the others, the choice between them depends mainly on two factors—cost and incidence of side-effects

With regard to cost we are satisfied that ferrous sulphate is the least expensive preparation of iron available (Davidson and Richmond 1958) With regard to side-effects, experiments on animals have shown that in *very large* doses ferrous sulphate is appreciably more toxic than comparable amounts of iron and ammonium citrate, and two to five times as toxic as ferrous gluconate (Hoppe et al 1955, Brown and Gray 1955) Accidental poisoning with ferrous sulphate, usually in children, has sometimes been fatal (Reissman et al 1955) It does not appear, however, that the symptoms of which patients complain when taking therapeutic doses of iron are simply milder forms of those caused by acute poisoning, since the latter are partly due to excessive absorption of iron (Reissman and Coleman 1955). For instance, constipation is the most common complaint of patients taking iron, whereas diarrhœa is an almost constant feature of ferrous-sulphate poisoning

Published reports of the incidence and severity of gastrointestinal intolerance to therapeutic doses of iron vary greatly

This variation is seen particularly with ferrous sulphate, whether given alone or with traces of other metals (molybdenum, cobalt, copper) Thus various authors have reported intolerance-rates ranging from 0 to 60% Many of the reports are difficult to assess, because inadequate information on dosage, number and type of patient, and definition of intolerance is given Some of the papers in which adequate data have been recorded are summarised in table I If the cases given very large doses of ferrous sulphate (360 mg of iron daily) are excluded, the incidence of intolerance in 367 patients receiving an average of 220 mg of ferrous sulphate daily is 4%, a figure comparable to that shown in table I as occurring after the ingestion of 210 mg of ferrous gluconate daily

In this analysis we have not taken into account the report by Talaga (1955), because the intolerance-rate of 60% in his series of patients was conspicuously different from that reported in all other trials included in table I in which comparable doses of iron were given

Study of the reports also shows that the iron content of the preparations of ferrous sulphate was usually larger than that of the other compounds, that the pills employed varied widely in colour, size, and type of coating, that the series of patients were not always comparable, and that the definition of "side-effects" varied from mild symptoms to a degree of intolerance necessitating cessation of treatment

It may be assumed that the enthusiasm shown by a doctor recommending treatment, and the statements which he makes to patients about the likelihood of side-effects, will also vary These factors can be eliminated only by arranging a trial in which pills with identical coating and the same iron content are given to matched groups of patients on the "double blind" principle—neither the patient nor the doctor knowing which preparation is being employed until after the results have been assessed

During such a trial carried out on antenatal patients by Kerr and Davidson (1958) a comparison was made between ferrous sulphate, ferrous gluconate, and inert tablets The incidence of gastrointestinal symptoms attributed by the patients to their pills was similar in the three groups It was felt that pregnant women might be unsatisfactory subjects for a detailed study of this kind, because they often suffer from constipation and heartburn, and because they spend a considerable amount of time sitting in queues at antenatal clinics, discussing their symptoms Accordingly a second double-blind trial was planned, using as subjects healthy non-pregnant young women The results are reported here

Plan of the Experiment

The purpose of the trial was explained to the nursing staff of the Royal Infirmary, Edinburgh, and 100 volunteers requested Each volunteer was given six packets of pills and asked to take them, in the dosage prescribed on the packets, after meals, from Monday to Friday during six successive weeks No pills were taken on Saturdays and Sundays, and at the end of each week a questionnaire was completed giving details of any symptoms experienced during the preceding week

TABLE I—INCIDENCE OF GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS REPORTED BY VARIOUS AUTHORS

Ferrous preparation	Dose (mg iron daily)	Trace metals added	Indication for treatment	No of patients	Intolerance-rate (%)	Author
Sulphate	200	Nil	Pregnancy	27	4	Devoe and Moses 1954
"	240	Nil	"	41	60	Talaga 1955
"	360	Nil	"	207	57	Gatenby and Lillie 1955
"	210	Nil	Hypochromic anæmia	25	13	O Sullivan et al 1955
"	360	Copper, manganese	Pregnancy	51	35	Benstead and Theobald 1952
"	180–240	Cobalt	"	58	0	Holly 1955
"	240	Molybdenum	"	75	1	Lund 1951
"	360	"	"	15	14	Benstead and Theobald 1952
"	360	"	"	91	44	Gatenby and Lillie 1955
"	240	"	"	24	0	Devoe and Moses 1954
"	240	"	"	18	6	Talaga 1955
" (white)	200	Nil	"	140	5	Edgar and Rice 1956
Gluconate	210	Nil	"	109	14	Gatenby and Lillie 1955
"	210	Nil	Hypochromic anæmia	25	4	O'Sullivan et al 1955
Succinate	210	Nil	" "	25	4	O Sullivan et al 1955
"	105	Nil	" "	150	<1	Gillhespy 1955
"	105	Nil	Pregnancy	49	2	Cope et al 1956
Calcium citrate	150	Nil	"	48	0	Talaga 1955

Six symptoms were mentioned specifically on the form—nausea, vomiting, heartburn, abdominal discomfort, constipation, and diarrhœa—and a space was left to record "any other symptoms" The volunteers were asked to describe only symptoms which they believed were due to the pills, they were not asked to grade their severity but merely to say whether they were severe enough to prevent their taking the full course of treatment prescribed for that particular pill If they were obliged to stop taking one pill on account of symptoms, they were asked to continue with the others according to schedule They were told that the first five packets contained iron pills of various types, some of which would change the colour of the stools while others would not The sixth packet was marked "control pills" and it was explained that these were given to make sure that the coating used on the other pills was not itself a cause of symptoms

The five "iron pills" contained ferrous sulphate, ferrous gluconate, ferrous succinate, ferrous calcium citrate, and lactose The last is hereafter referred to as the "unknown" control pill The pills known to the patient as the "control" pills also contained lactose, and were identical in appearance and composition to the "unknown" control pills

Careful consideration was given to the dosage of iron to be incorporated in the pills

It was essential that the daily iron intake should be the same irrespective of which preparation was being taken The usual dose of ferrous gluconate is one 300 mg (gr 5) pill and of ferrous succinate one 150 mg (gr $2^1/_2$) pill, each containing 35 mg of elemental iron, given three times a day, making a total of 105 mg of iron daily The dose of ferrous calcium citrate recommended by the manufacturers is two 300 mg (gr 5) pills each containing 25 mg of elemental iron, given three times a day, making a total of 150 mg of iron per day Ferrous sulphate, however, is usually prescribed as one 180 mg (gr 3) pill containing 60 mg of elemental iron, three times a day, making a total of 180 mg of iron daily At the outset a decision had to be made as to whether it was desirable to increase the dose of elemental iron in each ferrous gluconate and succinate pill to 60 mg—i e, about double the usual therapeutic dose—or to reduce the amount of elemental iron in each ferrous sulphate tablet from 60 mg to 35 mg The latter choice was made because evidence had been obtained by Kerr and Davidson (1958) that ferrous sulphate was effective when given in the smaller dose

Each ferrous-sulphate, gluconate, and succinate pill contained 35 mg of iron, the dose of these and of the "known" and "unknown" control pills was one, three times a day Ferrous calcium citrate could not be prepared in pills of the same size, with an iron content of 35 mg, it was therefore made up in pills containing 17 5 mg of iron, identical in other respects to the control pills, and given in a dose of two tablets three times a day To this extent the ferrous calcium citrate pills were distinguishable from the others, but, with this exception, the comparison was carried out as a double blind experiment, the key being opened only after the results had been analysed. The pills were identical in size, shape, colour, and coating

The volunteers were assigned at random to five groups which took the pills in different orders

103 nurses volunteered 7 failed to complete it for reasons unconnected with the pills (intercurrent illness, night duty, holidays) 3 others dropped out because they experienced unpleasant symptoms One of these complained of abdominal pain and diarrhœa, and another of constipation, while taking ferrous sulphate The third volunteer had various symptoms while taking ferrous calcium citrate, ferrous gluconate, and "unknown" control pills

The 93 volunteers who completed the trial were all healthy young women aged 18–30 years (mean age 21) The hæmoglobin level was not estimated routinely, but 23 volunteers when visiting the blood clinic to collect their pills asked that this estimation should be carried out Their hæmoglobin levels ranged from 11 7 to 15 5 g per 100 ml (79–105%), the mean being 13 9 g (94%) This suggests that most of the subjects were not significantly anæmic 11 had been treated with oral iron in the past, but none could recollect any untoward symptoms from this

Results

The replies given by the 93 who completed the trial are summarised in table II

In total incidence, "toxic effects" from the "unknown" control pills did not differ significantly from those accompanying any of the preparations containing iron, whether the slight or doubtful symptoms were

TABLE II—INCIDENCE OF ALL GASTROINTESTINAL SYMPTOMS IN 93 SUBJECTS WHO COMPLETED THE TRIAL

Iron preparation	1 No symptoms	2 Slight or doubtful symptoms	3 Symptoms +	4 Symptoms ++	5 Total with significant symptoms (3+4)	6 Total with no significant symptoms (1+2)
Ferrous sulphate	58	12	22	1	23	70
" gluconate	69	4	17	3	20	73
" succinate	59	13	19	2	21	72
calcium citrate	63	11	14	5	19	74
"Unknown control	65	8	18	2	20	73
'Known' control	91	0	2	0	2	91

+ = symptoms definite but treatment continued. ++ = symptoms severe enough to stop treatment with that pill

TABLE III—INCIDENCE OF SYMPTOMS ATTRIBUTED TO IRON PILLS

(Group A 20 subjects who complained of symptoms with "unknown" control pills Group B 73 subjects who did not complain)

Iron preparation	Total no	No with definite symptoms	Intolerance rate (%)
Group A			
Ferrous sulphate	20	10	50
" gluconate	20	8	40
" succinate	20	5	25
" calcium citrate	20	7	35
Group B			
Ferrous sulphate	73	13	18
" gluconate	73	12	16
" succinate	73	16	22
" calcium citrate	73	12	16

included in the analysis or not (P>0 05) Only 2 volunteers recorded symptoms while taking the "known" control pills, 1 complained of heartburn and 1 of constipation When the incidence of side-effects was calculated for the whole group of 103 (using the incomplete replies of the 10 nurses who failed to complete the trial) there was again no significant difference between iron preparations and "unknown" control pills

It was clear that factors other than iron were responsible for most of the "toxicity" reported by these volunteers One possibility was that a proportion of them were unusually suggestible, and developed symptoms whenever they took pills which they believed to contain iron If this were so, it would be important to exclude such subjects from consideration when comparing the iron preparations

To test this hypothesis the 93 who completed the trial were divided into two groups—the 20 nurses who complained of symptoms with "unknown" control pills (group A), and the 73 who did not (group B) Table III shows that there was more intolerance to iron-containing pills in group A than in group B, and in the case of ferrous sulphate and ferrous gluconate this difference was significant (P<0 05) In group B the intolerance-rates to the four iron preparations did not differ significantly from one another

Analysis of the individual symptoms reported with the various iron pills shows that no characteristic symptom complex resulted from taking any of the pills With each preparation, constipation and abdominal discomfort were the commonest symptoms, the incidence of all the others was less than 10%

11 of the subjects who did not complain of symptoms with control pills had symptoms with more than one of those containing iron 3 of them reported constipation with each of two preparations, but otherwise there was no consistency in the symptoms of which any individual complained Nobody reported symptoms with all four iron preparations There was therefore no evidence of the occurrence of true iron intolerance embracing all forms of oral iron

DISCUSSION

The importance of psychological factors in producing both beneficial and undesirable results from drug therapy is now widely recognised

Girdwood (1952) focused attention on this aspect of iron intolerance In a clinical trial of molybdenised ferrous sulphate he found that many patients who were intolerant of ferrous sulphate had no symptoms when taking the preparation containing trace amounts of molybdenum Realising that this might be partly due to the difference in appearance between the pills, he administered ferrous sulphate, in the form of white pills, to 16 patients who had previously developed gastrointestinal symptoms when taking exactly the same preparation in the form of green pills ('Fersolate') 14 of the 16 took white ferrous-sulphate pills without complaint

Edgar and Rice (1956) used similar white ferrous-sulphate pills in the prophylaxis of anæmia of pregnancy, and found a much lower intolerance-rate than most other investigators using the green pills

Two main factors contribute to this finding

Firstly, mild gastrointestinal disturbances, particularly constipation, are common in any group of young women, and particularly in the pregnant women, who in Great Britain form the majority of the patients receiving iron therapy There is a strong tendency for the patient to attribute these symptoms to any medicine she *is taking*, especially if she knows that it may have such effects This tendency may have been accentuated in the present trial since the volunteers were specifically asked to note any gastrointestinal disturbance, and their attention was directed to likely symptoms by the questionnaire That transient incidental symptoms were responsible for many of the "toxic effects" reported is suggested by the observation that more than half the nurses who complained of symptoms with "unknown" control pills had *no symptoms when taking* one or other of the iron preparations

Secondly, suggestible people can develop symptoms of psychological origin, not previously present, when taking pills which they believe will upset them

This phenomenon is observed in most clinical trials, and the proportion of subjects who exhibit it may be surprisingly high In a trial of phenoxybenzamine for the treatment of chilblains (College of General Practitioners 1957) 13% of the patients taking placebo pills complained of dizziness or other symptoms which they had been warned might occur with phenoxybenzamine In a similar long-term trial of tetracycline (Moyes and Kershaw 1957) 39% of those receiving *placebos complained* of diarrhœa

In the present investigation the incidence of symptoms in the group as a whole was almost the same, whether the iron was taken as ferrous sulphate, ferrous gluconate, ferrous succinate or ferrous calcium citrate Similar "toxic effects", however, were reported equally often after taking the "unknown" control pills which were thought to contain iron but in fact contained only lactose It is of great interest that with the "known" control pills (identical in every way with the "unknown") only 2 subjects reported symptoms This observation may be interpreted in two ways either (1) most of the subjects experienced no symptoms while taking the "known" control pills, or (2) the symptoms arose, but, because they could not be ascribed to the pills, were ignored or attributed to other factors

Our impression that the "toxic effects" of the pills were not due to iron is strengthened by our finding that no symptom or group of symptoms was constantly associated with any particular preparation of iron and that, when they were on iron therapy, none of the subjects consistently complained of symptoms distinguishable from those they reported when "unknown" inert pills were taken

It should be emphasised that the conditions in this trial were not identical with those in clinical practice

Firstly, the dose of iron chosen for the trial approximated closely to that used in practice when commercial preparations *of ferrous gluconate* and ferrous succinate are prescribed, but was about *half that usually* employed when ferrous sulphate is prescribed Secondly, the pills were given for only five days at a time (This period was thought long enough *for* symptoms due to gastrointestinal irritation to appear) Thirdly, this trial differed from previous therapeutic trials in that the people taking part in it were neither anæmic nor pregnant We would, however, point out that we obtained almost identical results in a similar trial on pregnant women (Kerr and Davidson 1958)

We conclude that a large proportion of the symptoms experienced during therapy with oral iron preparations is psychological in origin The possibility that some patients have true iron intolerance cannot be excluded, but the incidence of toxicity—at least with doses of 35 mg of iron three times a day—must be very low Among those whose complaints were confined to iron preparations, the symptom most commonly reported was constipation Other gastrointestinal effects were variable, and usually mild, and they were never reported by more than 12% of subjects

It will take a long time to dispel the popular belief that iron pills inevitably cause unpleasant side-effects, but reassurance and enthusiastic propaganda could do a great deal to reduce the "intolerance rate" Recently we have found it well worth while to explain to patients that the pills they are about to take have been tested in a blind trial and found to cause no more symptoms than pills containing sugar

Summary

1 Ferrous sulphate, ferrous gluconate, ferrous succinate, ferrous calcium citrate, and "known" and "unknown" control pills (containing lactose) were administered to 93 healthy young women in a double-blind trial The incidence of gastrointestinal symptoms attributed to the pills was assessed from the replies to a questionnaire

2 Virtually no toxic effects were reported from "known" control pills containing lactose, but the exactly similar "unknown" control pills, which were thought by the subjects to contain iron, produced as many side-effects as the pills which did in fact contain it

3 None of the four iron compounds was found to be significantly more "toxic" than inert pills containing lactose Hence it was concluded that intolerance to these iron preparations, in the dosage given, was mainly psychological in origin

We wish to express our thanks to the nurses who took part in the trial and to Miss Law, assistant lady superintendent, Royal Infirmary, Edinburgh, who helped to recruit the volunteers, to Dr Gordon Fryers, of John Wyeth and Brother, Ltd for the supply of ferrous sulphate, ferrous gluconate, and control pills, to Mr John Williams, of Calmic Ltd for the supply of ferrous succinate, and to Mr Reginald George, of Ortho Pharmaceuticals Ltd for the supply of ferrous calcium citrate, used in the trial

REFERENCES

Benstead, N , Theobald, G W (1952) *Brit med J* i, 407
Brown, R J Gray J D (1955) *Canad med Ass J* 73, 192
College of General Practitioners (1957) South East Scotland Faculty *Brit med J* ii, 1521
Cope, E , Gillhespy, R O , Richardson, R W (1956) *ibid* ii, 638
Davidson, L S P , Fullerton H W (1938) *Edinb med J* 45, 193
— Richmond, J R (1958) *Lancet* (in the press)
Devoe, R W , Moses, L E (1954) *Calif Med* 81, 304
Edgar, W , Rice H M (1956) *Lancet* i, 599
Gatenby, P B B , Lillie, E W (1955) *ibid* i, 740
Gillhespy, R O (1955) *Med Ill* 9, 147
Girdwood, R H (1952) *Brit med J* i, 599
Haler, D (1952) *ibid* ii, 1241
Holly R G (1955) *Obst Gyn N Y* 5 562
Hoppe, J O Marcelli, G M A , Tainter, M L (1955) *Amer J med Sci* 230, 491 and 658
Jasinski, B (1949) *Schweiz med Wschr* 79 1255
Kerr, D N S , Davidson L S P (1958) *Lancet*, ii, 483
Lund C J (1951) *Amer J Obstet Gynec* 62, 947
Moyes, E N , Kershaw, R A (1957) *Lancet*, ii, 1187
O Sullivan D J , Higgins P G , Wilkinson, J F (1955) *ibid* ii, 482
Reissman K R , Coleman, T J , Budai, B S , Moriarty, L R (1955) *Blood*, 10 35
— — (1955) *ibid* p 46
Storm Mathiesen H , Petersen, A M (1956) *Tidsskr norske Lægeforen* 76, 510
Talaga, E S (1955) *Obst Gyn N Y* 5, 201

ACCIDENTAL HYPOTHERMIA

A COMMON CONDITION WITH A PATHOGNOMONIC ELECTROCARDIOGRAM

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INDUCED hypothermia now plays an accepted part in surgery of the heart and brain and has therefore been studied a great deal by physiologists (Kayser 1957) Clinicians, however, have paid comparatively little attention to accidental hypothermia, and Rees (1958), who recently reported four cases, has stated that in clinical medicine it is uncommon

The electrocardiogram in preoperative hypothermia has features characteristic enough to be pathognomonic (Emslie-Smith 1956, Fleming and Muir 1957) As temperature falls, the heart-rate slows, and the intervals PR, QRS, and QTC all lengthen A conspicuous extra deflection appears at the junction of the QRS complex and the ST segment This "junction deflection" (J deflection) is slowly inscribed and is usually most obvious in lead V4, where it is directed upward In other leads the base of the QRS complex is widened In the vectorcardiogram these features are represented by an extra loop between the QRS and T loops (Emslie-Smith 1958) When the J deflection is large, the T wave may become inverted

Tomaszewski (1938) published the electrocardiogram of a vagrant dying from cold Since then the electrocardiogram in accidental hypothermia seems to have been recorded on eight occasions only (Wayburn 1947, Graybiel and Dawe 1948, Laufman 1951, Karnell *et al* 1955, Biorck and Johansson 1955, Rees 1958) Only a few of these records showed the characteristic J deflection, and Rees (1958) did not see it in the electrocardiograms of his patients

I have recently encountered eight cases of accidental hypothermia, and heard of another, in circumstances which suggest that the condition is very much commoner than is supposed In seven cases adequate electrocardiograms showed the pathognomonic pattern, in the eighth it was obscured by bundle-branch block

Case-reports

Case 1 —A mentally depressed woman, aged 50, was found unconscious It was thought that she had swallowed a large dose of carbromal and barbiturate She was cyanosed and deeply comatose, with shallow respirations occurring only three times a minute All her tendon-reflexes were absent, her systolic blood-pressure was 60 mm Hg, and her rectal temperature was 30 2°C (86°F)

An endotracheal tube was passed, and oxygen was given by artificial respiration with a closed circuit An intravenous infusion of plasma was started The electrocardiogram then showed sinus bradycardia (rate 47 a minute). Changes typical of hypothermia were present PR measured 0 16 sec., QRS 0 08 sec , and QTC 0 57 sec , a small, slowly inscribed, extra deflection was present between QRS and the early part of the ST segment (J deflection), it was directed upward in leads I, II, III, aVL, aVF, V4, and V6, and downward in lead aVR

The patient died after 48 hours' coma

Case 2 —A grossly myxœdematous woman, aged 75, was found naked and unconscious Her heart sounds were faint, blood-pressure 150/90 mm Hg, and respirations 20 a minute. There were no focal neurological signs Her rectal temperature was 27°C (80 6°F) The electrocardiogram showed sinus rhythm (rate 30 a minute) It was characteristic of hypothermia PR measured 0 19 sec , QRS 0 11 sec , and QTC 0 58 sec , in leads aVL, V4 and V5 a small J deflection was present between QRS

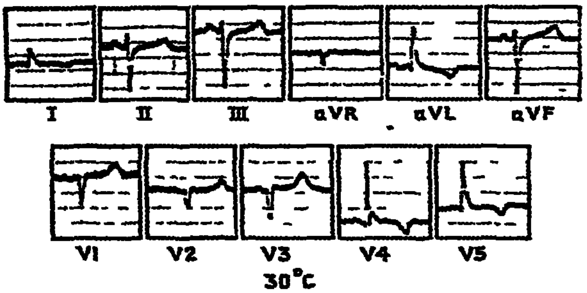

Fig 1—Electrocardiogram in case 3 with rectal temperature 30 C (86 F) Note QTc interval prolonged (0 53 sec.), typical J deflection prominent in lead V4, base of QRS widened in leads I, aVL, aVF, V5, and T inverted in leads I, aVL, V4, and V5

and the early part of the ST segment T was directed downward in leads I, II, III, aVF, V4, and V5, and upward in leads aVR and aVL. Despite gross myxoedema the amplitude of the complexes was not reduced R in lead I, for example, measured 1 35 mV

Warming and the administration of triiodothyronine were ineffective. The patient died about 12 hours after admission.

At necropsy the thyroid gland was small and fibrotic, and the plasma-cholesterol level was 550 mg per 100 ml, there was some hypertrophy of the left ventricle, and there was patchy atheroma of the coronary arteries without occlusion of the lumen

Case 3—A one-legged woman, aged 82, was found lying neglected and stuporous in front of an unlit fire She had a black eye on the left side, and radiography showed a small fracture above the left orbit She had multiple abrasions, and gangrene of the right foot Her blood-pressure was 120/100 mm Hg, and rectal temperature 30°C (86 F)

Electrocardiograms showed mechanical artefacts caused by muscular tremor There was sinus rhythm (rate 42 a minute) The typical changes of hypothermia were present PR measured 0 20 sec, QRS 0 05 sec, and QTc 0 53 sec, a typical large J deflection was present in V4, T was inverted in leads I, aVL, V4 and V5, there was widening, with ledging, of the base of QRS in leads I, aVL, aVF, and V5 (fig 1)

The patient died about 12 hours after admission. Necropsy showed ulcerating atheroma of the thoracic aorta and multiple small infarcts in spleen and kidneys The left ventricle was hypertrophied. The cerebral cortex was slightly atrophied

Case 4—A diabetic man, aged 80, who was well cared for at home, began to have hypoglycaemic attacks, for which he came to hospital His dose of insulin-zinc suspension was adjusted Two days after discharge he behaved oddly and fell He was put to bed and given sugar, but his manner remained peculiar all evening At 2 A.M. he "seemed to have settled", but at 7 A.M. he was found wet, half out of bed, and without bedclothes

He was stuporous, with corpse-like pallor and unusually firm subcutaneous tissues His blood-pressure was 115/50 mm Hg, and his respirations were 16 a minute His limbs were held rigid His tendon-reflexes were all present, but his muscles contracted slowly His rectal temperature was 25 75°C (78 3°F)

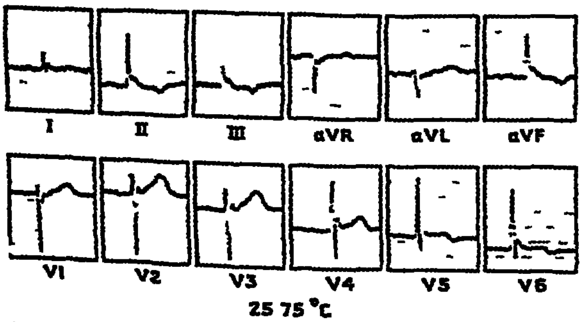

Fig 2—Electrocardiogram in case 4 with rectal temperature 25 75 C (78 3°F) Note QTc interval prolonged (0 54 sec) typical J deflection directed upward in leads I II, and V2–V6 and downward in lead aVR, base of QRS widened in leads III and aVF and T inverted in leads II, III, aVF, V5, and V6, and flat in lead I.

The electrocardiogram was distorted by a fine mechanical artefact caused by muscular tremor There was sinus rhythm (rate 48 a minute) The characteristic changes of hypothermia were present PR measured 0 24 sec., QRS 0 07 sec., and QTc 0 54 sec, there was a conspicuous J deflection, directed upward in leads I, II, and leads V2–V6, and downward in lead aVR, T was inverted in leads II, III, aVF, V5, and V6 and flat in lead I, there was widening of the base of QRS in leads III and aVF (fig 2)

The patient was given intravenous glucose and prophylactic penicillin and was heated under an electric blanket 24 hours later his rectal temperature was 31 75°C (89 2 F) and his physical state more normal His blood-sugar level was 134 mg per 100 ml and blood-urea level 73 mg per 100 ml The signs of hypothermia in the electrocardiogram were less conspicuous, but a J deflection was still present, directed upward in leads I, II, aVF, V5, and V6, and downward in lead aVR T was inverted in leads aVF and III The base of QRS was widened in leads III and V1

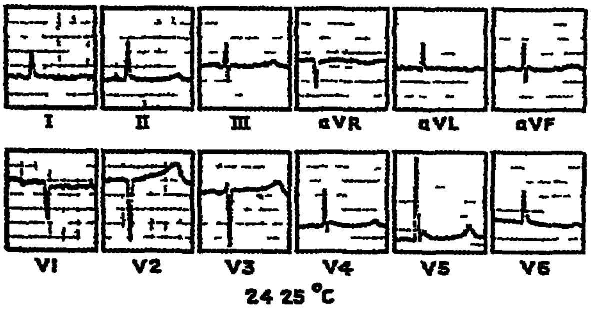

Fig 3—Electrocardiogram in case 5 with rectal temperature 24 25 C (75 6 F) Note QTc interval prolonged (0 60 sec.), typical J deflection in leads aVF, V4, and V5, base of QRS widened in lead V6, and T flat in lead aVL and diphasic in lead V6.

About 60 hours after admission the patient's temperature was 37°C (98 6°F), pulse-rate 100, and respirations 30 a minute Although no longer stuporous he was confused His temperature rose to 39 5 C (103 F), and signs of bronchopneumonia appeared. Electrocardiograms now indicated anterolateral myocardial ischaemia He died 5 days after admission.

Case 5.—Within a few weeks of beginning to live on her own, a woman, aged 72, was found lying unconscious on the floor Relations said she had become increasingly confused and breathless and had felt the cold badly She had occasionally been dizzy and had sometimes fallen.

She was cyanosed and comatose, with rectal temperature 24 25 C (75 6 F), and respirations 12 a minute, expiration prolonged and grunting Her radial pulse could not be felt, and no blood-pressure could be recorded. The outer halves of her eyebrows were thin, her protruded tongue was thick, and her skin was dry and scaly Her facial subcutaneous tissue was thick. All her limbs were rigid, but she grimaced and moved her arms slowly Her pupils reacted sluggishly to light Her tendon-reflexes were present, but her muscles contracted slowly Both her legs were oedematous, with large varices

The electrocardiogram was distorted by tremor but showed sinus rhythm (rate 36 a minute) There were characteristic changes of hypothermia PR measured 0 24 sec., QRS 0 06 sec., and QTc 0 60 sec, a J deflection was present in leads II, III, aVF, V4, and V5, T was flat in lead aVL and diphasic in lead V6, in lead V6 the base of QRS was widened (fig 3)

After the patient had been warmed all night, her rectal temperature had risen to 32°C (89 6 F) and she seemed better She answered simple questions slowly with a hoarse voice Her systolic blood-pressure was 60 mm. Hg, and pulse-rate 62 No cardiac murmurs were heard The electrocardiogram showed right bundle-branch block and ventricular ectopic beats Myxœdema was diagnosed, but despite the administration of cortisone and triiodothyronine she deteriorated and died

At necropsy the thyroid gland was small and fibrous There was aortic stenosis and incompetence, with left ventricular hypertrophy, and bronchopneumonia

Case 6 —A woman, aged 81, who lived alone, was thought by her neighbours to be unwell Her doctor found her unsteady, with slurred speech, wondered if she had taken too many sleeping tablets, and put her to bed Next day she was found, clad only in a nightdress, confused and cold, with a black eye On admission to hospital she was comatose, with a large contusion and laceration of the left supraorbital region Her rectal temperature was 27 5°C (81 5°F), respirations 16 a minute, and blood-pressure 120/80 mm Hg Her pupils reacted sluggishly to light Her limbs were rigid and flexed, and her tendon-jerks were present but typically slow She had a single generalised convulsion, with conjugate deviation of her eyes to the right Radiography showed no fracture of skull

The electrocardiogram showed considerable clockwise rotation of a vertical heart and sinus rhythm (rate 72 a minute) The record was characteristic of hypothermia PR measured 0 24 sec, QRS 0 04 sec, and QTC 0 49 sec, a J deflection was present in leads II, III, and aVF, T was flat, and the base of QRS was widened, in leads V7 and V8

After the patient had been warmed for four hours, her rectal temperature was 30°C (86°F) and atrial fibrillation was noted Later hemiplegia and upper-motor-neurone paralysis of the seventh cranial nerve appeared on the left side Lumbar puncture yielded normal cerebrospinal fluid under normal pressure The patient's temperature rose to 38 3°C (101°F), signs of bronchopneumonia appeared, and she died

Necropsy showed subdural hæmatoma in the right occipital region and atherosclerosis of the cerebral arteries

Case 7 —Every winter for about 14 years a woman, aged 64, had become cold and lethargic, with slowing of mental and bodily activities During these periods, which her relations described as " hibernation ", she was sometimes stuporous or even comatose, and she was often admitted to hospital, where various provisional diagnoses were made and different treatments given During a spell of cold weather in early spring she again became cold and retarded and was admitted to hospital

She was stuporous, answering simple questions with monosyllables only Although her eyebrows were thin, her pubic hair was thick, and she did not look frankly myxœdematous Her skin was cold and dry, and the subcutaneous fat felt doughy Her pupils reacted slowly to light Her muscular tone was increased, and, although her tendon-reflexes were not increased in amplitude, her muscles contracted slowly after percussion of the tendon Her pulse-rate was 60, and respirations were 13 a minute The first and second heart sounds were unduly widely separated Her blood-pressure was 118/70 mm Hg and her rectal temperature was 33°C (91 4°F) Her serum-cholesterol level was 420 mg per 100 ml, this fact strongly supported the diagnosis of hypothyoidism

The electrocardiogram was slightly disturbed by muscular tremor and showed considerable clockwise rotation of the heart There was sinus rhythm, with occasional ventricular ectopic beats The typical changes of hypothermia were present PR measured 0 18 sec, QRS 0 06 sec, and QTC 0 42 sec, there was a prominent J deflection in leads V2, V3, and V4, T was inverted in leads II, III, aVR, aVF, and chest leads V2–V5, and flat in leads I and V1, there was widening of the base of QRS in leads I, III, and aVL

Warming her slowly in an electric blanket raised her temperature to 37°C (98 6°F) over 24 hours, but her general condition deteriorated, and she became comatose, with blood-pressure 80/50 mm Hg Treatment with triiodothyronine and cortisone produced a steady improvement, but she developed pyrexia and signs of bronchopulmonary infection and died a week after admission

At necropsy the thyroid gland was small (10 g), the heart was dilated, and there was focal acute and chronic pancreatitis

Case 8 —A woman, aged 86, who lived alone, was noticed to be confused Next day she was found comatose, with shallow respirations 16 a minute, blood-pressure 50/30 mm Hg, and rectal temperature 26 5°C (79 7°F) She had severe kyphoscoliosis, with dullness on percussion of the left hemithorax, coarse crepitations were heard over the right side of her chest Her pupils were small and did not react to light Her right plantar response was flexor, there was no response on the left

The electrocardiogram showed sinus rhythm (rate 30 a minute) PR measured 0 44 sec, QTC 0 61 sec In leads I and aVL a tiny R was followed by a wide deep slurred S In lead V1 and V2 a small Q was followed by a wide slurred R and an inverted T, in leads V5 and V6 a large R was followed by a deep wide slurred S and upright T These findings were interpreted as evidence of right bundle-branch block, possibly with anteroseptal infarction However, lead V3 showed a small R, then a rounded larger deflection which might have been a J deflection, T was inverted Lead V4 showed a larger R followed by a smaller rounded deflection (possibly J) and an inverted T Leads aVF and III showed what would have been interpreted, in the absence of right bundle-branch block, as the J deflection and inverted T of hypothermia

Warming was begun, but the patient died a few hours after admission

Discussion

In patients made hypothermic before operations on the heart or the brain a temperature of 28–30°C is achieved by elaborate medication and cooling Seven of my patients with accidental hypothermia had rectal temperatures between 30 2°C and 24 25°C (mean 27 2°C, S D 2 2)

Six of the patients were admitted to hospital within two winter months, and in all of them accidental hypothermia was diagnosed by physicians who had already taken special interest in the subject In none of the patients, however, was the actual depth of hypothermia appreciated until the accurate rectal temperature was taken by a laboratory thermometer or a thermistor recorder These facts suggest that the condition is very much commoner than is generally supposed, and that it is often unrecognised despite distinctive clinical features and a pathognomonic electrocardiogram

Rees (1958) has stated that hypothermia is a hazard of the extremes of life, and it is significant that, if the case of suicide is excluded, the mean age in this series was 77 (S D 6 9) Five of the patients lived alone, and this fact, too, is important, although case 4 shows that hypothermia can develop rapidly even without neglect It is clear from the case-reports that a British bedroom in winter is cold enough to make an elderly person with impaired cerebral function severely hypothermic, especially if he lies wet and partly clad

The clinical effects of hypothermia in man are characteristic (Alexander 1946) The patient has a waxy pallor, but the superficial veins are not necessarily collapsed The respirations are slow, with prolonged expiration The heart beats slowly, the blood-pressure may be low, and atrial fibrillation may develop Consciousness is clouded or lost There are muscular rigidity and tremor, and the tendon-reflexes are characteristically delayed and prolonged, but not diminished The pupils are dilated, and their reaction to light is poor At lower temperatures rigidity and tendon-reflexes disappear, respiration ceases, and death takes place usually when the temperature falls to 24–26°C, one patient has survived a temperature of 18°C (Laufman 1951) Most of the features were present in all my patients Although shivering was not often evident clinically, a fine muscular tremor produced an almost constant mechanical artefact in the electrocardiogram

It is important to recognise the clinical picture of hypothermia because it may disguise that of the underlying condition and thus delay full diagnosis and adequate treatment

The changes in the electrocardiogram found in various degrees in seven of my patients are identical with those constantly found in induced hypothermia in patients with normal hearts (Emslie-Smith 1956) and analogous to those seen in experimental hypothermia in dogs (Emslie-Smith et al 1958) The lengthening of the RR, PR, QRS, and corrected QT (QTC) intervals, the presence of the typical J deflection, with or without inversion of T, in leads related to the left ventricle, and the widening of the base of QRS in other leads, together constitute a pathognomonic pattern. The J deflection is almost always most conspicuous in left chest leads, especially lead V4 If adequate electrocardiograms with chest leads are not recorded, the J deflection may be missed, this is probably why it has not previously been recorded in accidental hypothermia with any constancy

Atrial fibrillation developed at a mean temperature of 28 9°C in six of ten patients with normal hearts during the production of preoperative hypothermia (Emslie-Smith et al 1958) By contrast it developed in only one of the eight cases of accidental hypothermia

The finding of the typical pattern in the electrocardiogram of a stuporous patient should suggest hypothermia Thus in case 3 the diagnosis was initially made from an electrocardiogram recorded to exclude a cardiac infarct or heart-block. It is, of course, easier to take the rectal temperature with a laboratory thermometer than to record the electrocardiogram, and probably the best way to diagnose accidental hypothermia is to remember the fact that it may complicate any state of impaired consciousness in an elderly patient

Summary

Accidental hypothermia has recently been diagnosed nine times in elderly patients in circumstances which suggest that it is much commoner than is generally supposed

The electrocardiogram showed a pattern pathognomonic of hypothermia in seven of the eight cases in which it was recorded in the eighth case the typical features were masked by bundle-branch block

The RR, PR, QRS, and QTC intervals were lengthened The characteristic J deflection of hypothermia was present in leads related to the left ventricle, when it was conspicuous, T was sometimes inverted In other leads the base of QRS was widened These changes were identical with those constantly seen in induced hypothermia in patients with normal hearts and analogous to those found in experimental hypothermia in dogs

Failure to use adequate leads, especially left chest leads, probably explains why this pathognomonic pattern has not been constantly found in accidental hypothermia

I wish to thank Prof I G W Hill, Mr Walter Campbell, Dr Robert Semple, Dr J M Stowers, and Dr R R Andrew for permission to study and report these cases

REFERENCES

Alexander, L. (1946) The Treatment of Shock from Prolonged Exposure to Cold, Especially in Water C.I O S Target No 24 Medical, G2 Division SHAEF (Rear) A P O 413
Bjorck, G., Johansson B (1955) *Acta physiol scand* 34, 257
Emslie-Smith, D (1956) *Australasian Ann Med* 5, 62
— (1958) *Brit Heart J* 20 175
— Sladden, G E., Stirling, G R. (1958b) *ibid* (in the press)
Fleming P R Muir F H (1957) *ibid* 19 59
Graybiel, A Dawe C. J (1948) U S N School of Aviation Medicine and Research Pensacola, Florida Project No NM 001 019
Karnell J., Lund F., Philipson, J (1955) *Nord Med* 54, 1867
Kayser C. (1957) *Ann Rev Physiol* 19 83
Laufman H (1951) *J Amer med Ass* 147, 1201
Rees, J R. (1958) *Lancet*, i, 556
Tomaszewski, W (1938) *Arch Mal Cœur*, 31, 525
Wayburn, E. (1947) *Arch intern Med* 79, 77

TRIAMCINOLONE

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Since the clinical use of the Δ^1 analogues of cortisone (prednisone and prednisolone) was first reported by Bunim et al in 1955, further efforts have been made to produce analogues which would have equal or greater efficiency as anti-inflammatory agents but fewer unwanted effects, particularly gastroduodenal ulceration The advantage of the Δ compounds was that they caused less salt and water retention than cortisone or hydrocortisone, while being clinically effective in approximately a fifth of the dose It was not long before new compounds appeared, and at the 9th International Congress of Rheumatology in Toronto last year the clinical effects of two more were reported—namely, triamcinolone (16-α-hydroxy, Δ^1, 9-α-fluorohydrocortisone) (fig 1) by Freyberg et al (1957) and medrol (6-methyl prednisolone) by Boland and Liddle (1957) The former substance is the subject of this report

Fried (1955) found that substitution of a fluorine or chlorine atom at C9 in the hydrocortisone molecule produced an increase in the glucocorticoid action and a greater increase in mineralocorticoid or sodium-retaining effect Apart from external application for skin disorders, this substance, 9-α-fluorohydrocortisone (fludrocortisone), is now used only in salt-losing cases of Addison's disease or after adrenalectomy In 1953 Hirschmann et al reported that, by adding a hydroxyl group to deoxycortone (Doca) at C16 in the α position, the characteristic salt-retaining activity of this substance was eliminated Three years later Bernstein (1956) reported that by adding a 16-α-hydroxyl group to the powerful 9-α-fluorosteroids their sodium-retaining potency was lost without decrease of glucocorticoid activity Addition of the 16-α-hydroxyl group not only failed to produce sodium retention, but actually caused sodium excretion and diuresis while glucocorticoid activity was retained This particular virtue did not impress us as constituting a great clinical advance on prednisone or prednisolone, except perhaps for patients with cardiac decompensation who were unable to tolerate the former substances What interested us more was the suggestion in early reports that certain side-effects—i.e, peptic ulceration, mental disturbances, and osteoporosis—were less with triam-

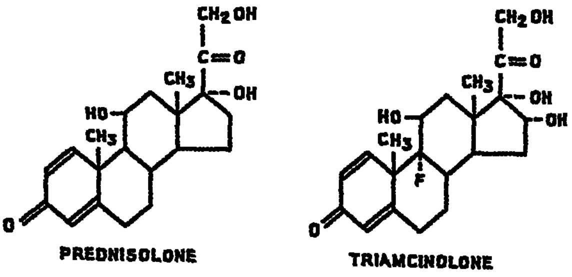

Fig 1—Prednisolone and triamcinolone.

was there any significant alteration in sedimentation-rate or finger tenderness In 11 patients subjective estimation of pain and stiffness was unchanged, 3 improved on prednisolone, and 11 on triamcinolone, but in only 5 was the improvement with triamcinolone more than slight Grip measurement was unchanged in all but 5 who improved on triamcinolone Finger swelling was also unchanged except in 5, who also improved on triamcinolone 7 patients had indigestion, in 3 it improved on triamcinolone, in 3 it became worse, and in 1 it was unchanged There were no acute "rebound" symptoms on transfer from prednisolone to triamcinolone or vice versa No significant weight changes occurred with either drug, though 1 patient had a consistently increased urinary output on triamcinolone, and 1 noticed diminished swelling not only in the affected joints but also in a swollen (previously thrombosed) leg In the case of psoriatic arthropathy the skin condition improved only with triamcinolone, and then strikingly 1 diabetic passed more sugar on triamcinolone than on prednisolone, and the blood-sugar level rose with triamcinolone 3 patients noticed hot feelings in the face and neck after meals only when taking triamcinolone In 2 patients who had had prednisolone for over two years, large striæ appeared on the abdomen within fourteen and twenty-one days of changing to triamcinolone Our patients on triamcinolone did not complain particularly of anorexia, headache, and lassitude, which have been reported by other observers About half the patients preferred triamcinolone to prednisolone, but the difference was slight except in 5 This may have been partly because a differently shaped tablet gave the impression of a new form of therapy Patients with rheumatoid arthritis are an optimistic group 3 cases are of particular interest

Case 26—A woman, aged 58, with a thirteen-year history of rheumatoid arthritis, had had steroid therapy for six years Recently, on prednisone 5 mg q d.s , vascular-necrotic lesions appeared on the hands and feet On May 5, 1958, she was given triamcinolone 4 mg q d.s , with an estimated subjective improvement of 15% A week later she had an episode of vomiting, possibly dietetic in origin, and was put back on to prednisone On May 24 triamcinolone 4 mg t d s was again substituted, and in the early hours of May 29 a gastric ulcer perforated During operation, which was successful, she had intramuscular cortisone in high dosage, and she has since remained well on oral hydrocortisone 60 mg daily

Case 27—A housewife, aged 54, developed severe and disabling rheumatoid arthritis in 1954 Cortisone 75 mg daily produced some improvement initially, and she has taken steroids ever since Her condition has gradually deteriorated though there was a temporary improvement when prednisolone was given in 1955 A year later a lumbar vertebra collapsed because of osteoporosis, meanwhile a moon-face was becoming more noticeable In April, 1958, triamcinolone 12 mg daily was substituted for 15 mg of prednisolone Since then her moon-face has become worse, and prominent striæ have appeared on the flanks and both breasts

Case 23—A woman, aged 38, with four months' history of acute rheumatoid arthritis was treated in hospital with prednisolone 5 mg b d., and improved greatly Five months later she became pregnant, and the rheumatoid arthritis worsened steadily in spite of increase of prednisolone to 17 5 mg daily, which caused mild indigestion She was again admitted to hospital and after a week there was little improvement Triamcinolone 14 mg daily was started, and during the next week there was a 50% improvement in her general condition, with a 25% increase in grip and reduction in finger swelling by 19 ring sizes The indigestion subsided.

Comment—This case illustrates the definite improvement in some patients who are transferred to triamcinolone Pregnancy apparently caused this patient's relapse This is the reverse of what is usually seen, but such cases are not uncommon

Systemic (Disseminated) Lupus Erythematosus

3 patients with systemic lupus erythematosus have been treated for periods of two to eight weeks on triamcinolone

Case 28—In 1949 a housewife, now aged 55, developed what was thought to be rheumatoid arthritis Cortisone therapy was begun two years later In 1954, following its abrupt withdrawal, she became acutely ill, with vomiting, abdominal pain, and fever, and lupus erythematosus cells were found in the blood There was a good response to prednisolone, which she took throughout 1957—usually 15 mg daily in divided doses—but there were several episodes of vomiting when it became necessary to increase the dose. Despite rigid salt restriction, she gradually became moon-faced and hypertensive

At the end of 1957 she developed severe and persistent back pain. In February, 1958, X-ray films of the spine were satisfactory, and her daily dose of prednisolone was increased to 25 mg Two months later it was reduced gradually to 15 mg daily, and then triamcinolone 12 mg daily was substituted Her back pain, however, became worse, and in May there was gross radiographic osteoporosis, with crush fractures of vertebræ and fractured ribs She has now had triamcinolone for eight weeks, her face is becoming more moon-like and striæ have appeared on her flanks

Comment—The osteoporosis was probably associated with increased prednisolone dosage There is no evidence that triamcinolone is alleviating the features of Cushing's syndrome, and it may be making them worse

The treatment of 2 other patients with disseminated lupus erythematosus has also been changed from prednisolone to triamcinolone and back to prednisolone without any significant alteration in their condition

Ulcerative Colitis

In 2 patients with ulcerative colitis 12 mg of triamcinolone daily was substituted for 15 mg of prednisolone Triamcinolone was continued for a week, and then prednisolone was given again In both cases the patients' subjective wellbeing, the number of stools and their consistence, and the amount of bleeding remained unaltered

Discussion

On the results of this short-term survey there seems little to choose between triamcinolone and its predecessors in the treatment of rheumatoid arthritis In our small series there was no real difference in aggravation or amelioration of dyspeptic symptoms, for 3 patients improved and 3 worsened when given triamcinolone The most important of all the so-called side-effects of steroid therapy—namely, dyspepsia with or without peptic ulceration—is not a fundamental or common feature of idiopathic Cushing's syndrome The possibility remains that variations of the cortisone molecule may result in the production of a therapeutically effective glucocorticoid with a lower incidence of gastroduodenal side-effects Long-term studies will reveal whether there is any appreciable diminution in incidence of these side-effects with triamcinolone or not

Two serious reactions—multiple crush fractures of vertebræ, and perforation of a peptic ulcer—were seen in our series on triamcinolone As both patients had been receiving full dosage with prednisolone for a long time before, one cannot say which steroid was particularly at fault, though in the former the period of increased prednisolone dosage was probably responsible

What then are the advantages, if any, of this new substance? Triamcinolone is another effective steroid with no particular virtue except that it does not cause salt and water retention. It appears to have certain mild side-effects unlike those seen with the previous Δ compounds, but, apart from postprandial flushing, these were not seen in our present small, short-term series The incidence of serious side-effects will have to be assessed on larger numbers

Where there was any advantage in changing from one drug to another it usually lay with triamcinolone, but the difference was small In a few cases objective physical signs improved on triamcinolone, but again the differences were usually slight

Summary and Conclusions

The treatment of 24 patients with rheumatoid arthritis and 1 with psoriatic arthropathy was changed from prednisolone to triamcinolone and (after a period of five to seventy days) back to prednisolone The dose ratio of triamcinolone to prednisolone was 4/5 Of these 25 patients, 11 preferred triamcinolone to prednisolone, 3 preferred prednisolone to triamcinolone, and 11 were indifferent

Measurement of sedimentation-rate and digital tenderness remained unchanged Finger swelling and grip strength altered in only 5 patients, each of whom improved on triamcinolone

There were no acute "rebound" symptoms on changing to either drug In only 5 cases was subjective improvement more than slight—in each case in favour of triamcinolone

Of 7 patients who complained of dyspepsia on prednisolone, 3 improved when transferred to triamcinolone, and 3 deteriorated

In 3 cases previously treated with prednisolone for over two years abdominal striæ appeared within three weeks of changing to triamcinolone 3 patients noticed postprandial flushing on triamcinolone, but not on prednisolone

The case-histories are presented of 3 patients with rheumatoid arthritis and 1 with systemic lupus erythematosus 2 others with the latter disease and 2 with ulcerative colitis were given triamcinolone without any change in their condition

Although triamcinolone does not differ greatly in its therapeutic action or in its undesirable side-effects from prednisolone it is useful to have another effective steroid available

Our thanks are due to the Lederle Laboratories Division of the American Cyanamid Company for supplies of triamcinolone ('Ledercort')

REFERENCES

Bernstein, S (1956) *J Amer chem Soc* 78, 5693
Berntsen, C A, Jr, Freyberg, R H, Kammerer, W H, Hellman, L (1957) Paper presented to the New York Rheumatism Association, April, 1957
Boland, E W, Liddle, G W (1957) *Ann rheum Dis* 16, 297
Bunim, J J, Pechet, M M, Bollet, A J (1955) *J Amer med Ass* 157, 311
Fried, J (1955) *Ann N Y Acad Sci* 61, 573
Freyberg, R H, Berntsen, C A, Jr Hellman, L, Gallagher, T F (1957) *Proc 9th int Congr heum Dis* p 79
Hart, F D, Clark, C J M, Golding, J R (1955) *Lancet*, ii 998
Hellman, L, Zumoff B, Schwartz, M K, Gallagher, T F, Berntsen, C A, Freyberg, R H (1957) *Ann rheum Dis* 16, 141
Hirschmann H Hirschmann, F B, Farrel, G L (1953) *J Amer chem Soc* 75, 4962
Sherwood H, Cooke, R A (1957) *J Allergy*, 28, 97

TRIAMCINOLONE ARTHRITIS?

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Triamcinolone was synthesised by Bernstein et al (1956) Early clinical studies have shown it to be therapeutically active in many conditions previously known to respond to cortisone, prednisone, and prednisolone (Hellman et al 1957, Sherwood and Cooke 1957, Rein et al 1957), and its therapeutic potency has been assessed as twice that of prednisolone (Sherwood and Cooke 1957)

When a supply of triamcinolone became available in Singapore, its clinical value was assessed in fourteen patients with various different conditions requiring corticosteroid maintenance therapy All had been receiving optimal doses of prednisolone, as determined by trial and error, with individual adjustments to give the best therapeutic response without producing any important side-effects Three of these patients had rheumatoid arthritis and two had systemic lupus erythematosus None of the others had ever noticed pain or stiffness in their joints, yet three of them developed arthritis, apparently as a result of the administration of triamcinolone This complication has not been described previously

Case-reports

Case 1.—A European woman, aged 23, had thrombocytopenic purpura She gave a 3 months' history of bruising and of menorrhagia Her hæmorrhagic diathesis responded well to prednisolone therapy, but a daily dose of 5 mg was necessary The only objective side-effects of this treatment were pronounced hirsutism and slight acne, but on questioning she stated that her libido was increased and orgasms were facilitated

After 6 months prednisolone was stopped and she was given triamcinolone 2 mg daily Within 24 hours she developed "flitting rheumatic pains" in her left shoulder, right elbow and wrist, and both feet She had no fever, tachycardia, or excessive sweating The erythrocyte-sedimentation rate (E S R) was 5 mm (Westergren) The administration of triamcinolone was continued and she was given codein co *B P* 2 tablets every 4 hours The pains decreased over the next 2 days and the analgesic tablets were discontinued After a month on triamcinolone her fingers showed swelling, typical of early rheumatoid arthritis, around the metacarpophalangeal and proximal interphalangeal joints The range of movement of her shoulder, knee, and elbow joints were all diminished The E S R was still 5 mm During the same period the thrombocytopenia recurred and she again began to bruise easily

When triamcinolone was replaced by prednisolone 10 mg daily, the swelling and stiffness of her joints rapidly disappeared, the thrombocyte-count increased, and she ceased bruising easily

Case 2—An Indian girl, aged 17, had 6 years' history of progressive bronchial asthma She was stunted and pigeon-chested Initial treatment with cortisone produced a definite improvement, but if the dose was reduced below 100 mg daily she had severe asthmatic attacks She developed a moon-face and mild hypertension of 135/90 mm Hg After 6 months the cortisone was replaced by prednisolone, initially 20 mg daily, but it was possible to reduce this to 10 mg daily over a period of 7 months without precipitating asthma During this period she grew 3 in taller, gained 12 lb in weight, and developed a good physique Her blood-pressure fell to 125/80, but her facial rounding remained She also developed acne and hirsutism, and noticed that her clitoris was enlarging

Prednisolone was replaced by triamcinolone, and on a daily dose of 4 mg she remained free of serious asthma for 4 weeks, but after 5 or 6 days she began to develop severe pains in her arms and legs, and noticed that her fingers were becoming stiff

Her right leg was particularly painful and examination revealed a tender nodule in the lateral head of the gastrocnemius. Her fingers showed swelling of the proximal and middle phalangeal joints, and the movements of her wrists, elbows, shoulders, hips, and knees were all limited by pain.

The triamcinolone was stopped and she was again given prednisolone 10 mg daily. The joint pains and stiffness disappeared in 2 days and a week later her fingers were normal.

Case 3.—An Indian woman, aged 21, had a 5-year history of bronchial asthma. This was controlled by cortisone 100 mg daily, but, during 7 months' holiday in India, her weight increased from 103 lb to 164 lb (height 63 in.) and she developed a very pronounced moon-face, slight dependent œdema, and a blood-pressure of 130/90 mm Hg. On a slimming regime and replacement of cortisone by prednisolone 10 mg daily, she slowly lost weight, her face became thinner, and her blood-pressure fell to 120/80. Her asthma was controlled by this dose, but she developed severe acne and hirsutism. Another complication was a vulval abscess, which responded to penicillin. It was found that her clitoris was unusually large.

Prednisolone was replaced by triamcinolone, and on a daily dose of 4 mg she remained free of asthma for 7 weeks. After 5 weeks, however, she complained that her legs seemed weak and she had pain in her knees. No objective evidence of arthritis was found, but, when the triamcinolone was stopped and she started on prednisolone again, the pain and weakness ceased.

Discussion

The onset of arthritic symptoms in three out of nine patients (who had no previous history of arthritis) when treated with triamcinolone instead of prednisolone strongly suggests that the change of therapy was responsible. The first two patients developed the typical appearances of early rheumatoid arthritis, and no other predisposing cause, such as infection or climatic change, was evident. All three were young women whose previous prednisolone therapy had produced virilising side-effects, and this may be significant. Two other women showing these side-effects, one with advanced rheumatoid arthritis and the other with systemic lupus erythematosus, had severe exacerbations of their joint symptoms when given triamcinolone, but this might have been merely due to inadequate dosage with corticosteroids, which often produces such relapses.

Possibly the arthritic symptoms in these three patients were primarily the result of prednisolone withdrawal. This seems unlikely since the use of prednisolone in many conditions in Singapore has not precipitated such symptoms, unless the patients had arthritis before the initial administration of corticosteroids. The remaining possibility is that triamcinolone directly caused an arthritic syndrome resembling, if not identical with, rheumatoid arthritis. It would be interesting to give the three patients another course of triamcinolone, to see whether they again develop arthritis, but they have not agreed to such a trial, and this unexpected finding must await further confirmation before its true significance can be assessed.

Apart from the development of arthritis, the results of triamcinolone therapy in this small series of patients were highly promising. In some cases its therapeutic efficiency was superior to that of prednisolone. The potency of triamcinolone was usually greater than that of prednisolone, though there was considerable variation in the equivalent dosages of the two corticosteroids in different patients.

Summary

Fourteen patients, previously maintained on prednisolone therapy for various conditions, were given triamcinolone. Of nine with no previous history of joint symptoms, three developed arthritis, and their histories are reported.

In two patients the condition resembled acute rheumatoid arthritis. It is suggested that arthritis may be a side-effect of triamcinolone therapy.

I am grateful to the Lederle Laboratories Division of the American Cyanamid Company for providing the triamcinolone ('Ledercort').

REFERENCES

Bernstein, S., Lenhard, R. H., Allen, W. S., Heller, M., Littell, R., Stolar, S. M., Feldman, L. I., Blank, H. H. (1956) *J. Amer. chem. Soc.* 78, 5693.

Hellman, L., Zumoff, B., Schwartz, M. K., Gallagher, T. F., Berntsen, C. A., Freyberg, R. H. (1957) *Ann. rheum. Dis.* 16, 141 (abstract).

Rein, C. R., Fleischmajer, R., Rosenthal, A. (1957) *J. Amer. med. Ass.* 165, 1821.

Sherwood, H., Cooke, R. A. (1957) *J. Allergy*, 28, 97.

SLIPPING OF THE UPPER FEMORAL EPIPHYSIS

A PLEA FOR URGENCY

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UNTIL recently the standard treatment of slipping of the upper femoral epiphysis was often traction in bed for six months or more. This gave relief from weightbearing, but in a large proportion of patients it did not achieve reduction. In a few cases the deformity even increased. In addition, at the end of this period the limbs were so weak, and sometimes so stiff, that they could ill support a heavy child whose weight had not decreased while lying in bed. Fusion across the epiphyseal line had been accelerated, but only at the expense of strength and function.

Surgical Treatment

Before 1929 this condition had frequently been treated by manipulation and plaster immobilisation, but a paper by Carnitz, which showed the results of manipulation, brought a sharp change in policy.

In 1938 Wilson, of the Hospital for Special Surgery, New York, described good results in 9 cases in which a Smith-Petersen pin had been inserted across the epiphyseal line. This operation produced equally good results in other clinics, so that internal fixation became accepted as a standard treatment for minor degrees of slip. The method has the limitation that it cannot be used when the displacement exceeds one-third of the maximum, but, with this proviso, it is a valuable procedure. It immediately stabilises the epiphysis, it prevents further slipping, and it accelerates fusion at a favourable age and at a level where interference with limb length is not serious.

With proper technique the operation is simple to perform and the patient has to be immobilised for no longer than it takes the wound to heal. A child can return to school after three weeks. More recently Smith-Petersen's trifin nail has been criticised as being unnecessarily large and traumatic and Hall (1957) has shown that smaller pins are equally effective and less likely to damage the vessels of the upper end of the femur.

Once the epiphysis has become dislodged, it is liable to go on slipping. Minor slips can be dealt with easily and satisfactorily, but major ones, if irreducible, have a very different prognosis. Left alone, these hips develop an adduction and external-rotation deformity, their range of movement will diminish, and there will be shortening and

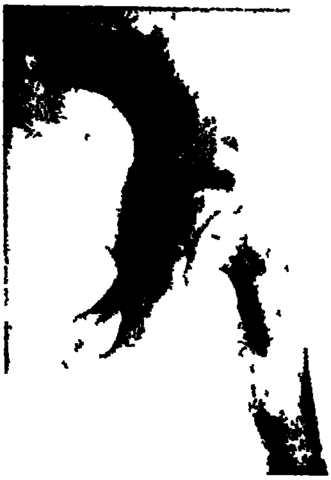

Fig 1—Severe, irreducible deformity

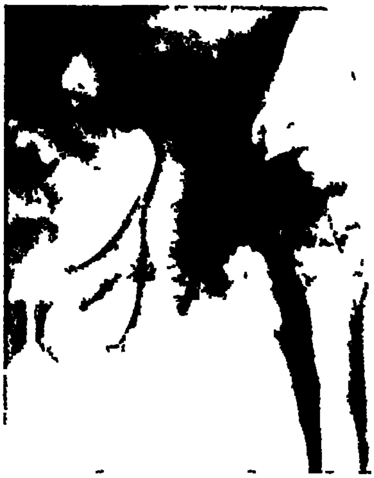

Fig 2—Osteoarthritic changes of untreated adolescent coxa vara

liability to premature osteoarthritis (figs 1 and 2) To such inactive treatment surgery is the only alternative but none of the operations employed is uniformly satisfactory

Groups of Patients

In the first group are adolescents with minor slips They should be regarded as surgical emergencies Immediately the condition is diagnosed the patient must cease to bear weight, and the surgeon must not rest content until the epiphysis is safely stabilised by pinning Once this has been done, it may be justifiable to assume that the hip-joint has been saved

Patients with acute traumatic displacement comprise the second group They should be treated by immediate reduction and simple pinning Provided that treatment is started while the epiphysis is still mobile, replacement is not difficult A difficult manœuvre—where force has to be used—is liable to damage further the already precarious blood-supply, and this may lead to stiffening Reduction is obtained by traction in internal rotation for two or three days, followed by gentle replacement under a general anæsthetic

The third group of patients are those who have a severe, irreducible deformity They all started in the first or second group but they were either not recognised or not treated in time

Causes of Delay

It was the long interval between the onset of symptoms and the beginning of surgical treatment which prompted me to refer to the notes of 45 cases treated under my care during the past ten years From this review two significant facts emerged. The average time between the onset of symptoms and the diagnosis was 26 6 weeks The average time between diagnosis and admission for definitive treatment was 3 8 weeks (This second figure includes the time spent by some patients undergoing treatment by bed rest and traction before their transfer to an orthopædic unit for pinning)

The causes of the delay were as follows

1 Failure of the patient to recognise and report symptoms

2 Failure of parents, schoolteachers, or games staff to recognise and report symptoms

3 Delay in clinical diagnosis

4 False radiological reassurance

5 Lack of realisation of the urgency of treatment by the referring doctor, or by the hospital clerical or surgical staff

It is unlikely that anything can be done to shorten the delay which is due to the adolescent not reporting his symptoms They are often slight, and his attitude is understandable, even admirable Failure of the parents or of the school staff to appreciate the significance of such symptoms is also understandable the condition is so uncommon and so difficult to recognise that it would be inappropriate to burden the public with medical propaganda for wider recognition It is unfortunate that by far the greatest delay occurs for these two reasons

Delay in Clinical Diagnosis

Even to the clinician, however, slipping of the epiphysis may be a difficult diagnosis It affects two types of patients, the fat type with hypogonadism and the long-limbed type who is passing through a phase of rapid growth It is slightly more common in boys In girls the commonest age of onset is twelve, and in boys thirteen, but the trouble may start at any time between nine and cessation of growth

The symptoms are invariably pain, a limp, or both The pain is sometimes localised to the hip, but more often it is referred to the lower anterior part of the thigh, or to the knee There is generally no other complaint and the patient may have continued to play games, however strenuous Examination of the hip will show limitation of abduction, of flexion, and of internal rotation, depending on the degree and the direction of the slip

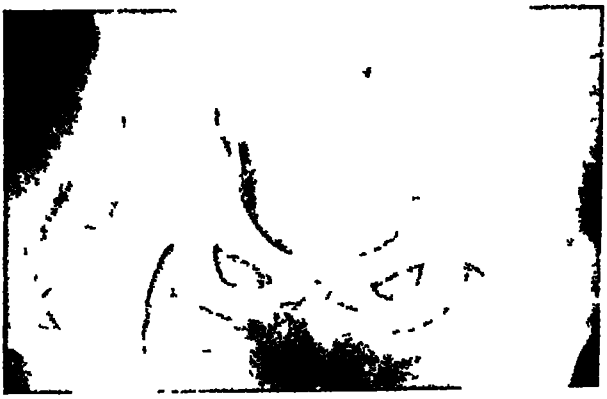

Fig 3—Anteroposterior view of hips, showing very little evidence of slip on right side

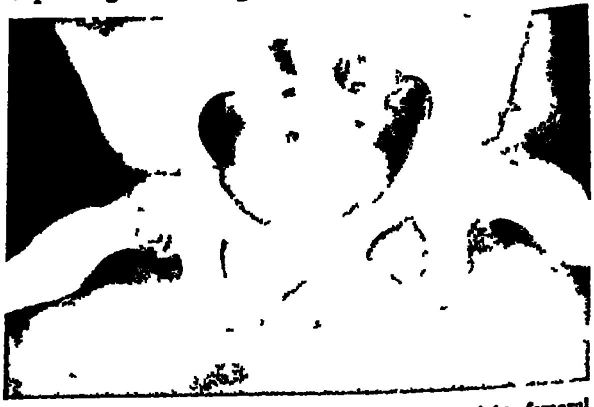

Fig 4—Same case, showing undoubted slip of right femoral epiphysis

Fig 5—Epiphysis stabilised by pinning

In severe cases there will be considerable flexion, adduction, and external-rotation deformity with true and apparent shortening The great trochanter will be displaced towards the pelvis It is rational to submit any child or adolescent who complains of pain in the hip or knee to X-ray examination of the hip-joints

Delay in Radiological Diagnosis

In a surprising number of cases referred for X-ray examination normal results are returned In this series such false radiological reassurance was the cause of delay in 7 cases Omission to take a lateral view was the reason for the mistake Often an anteroposterior view will show very little abnormality, whereas a lateral view will clearly demonstrate early slipping (figs 3–5)

The Urgency

Even when the condition is suspected or diagnosed, the urgency of treatment is often not recognised There may be delay in referring the patient to the appropriate clinic, or a distant appointment may be accepted by the practitioner or by the receiving-room or clinical staff

Slipping of the upper femoral epiphysis should be recognised as a surgical emergency, and admission to hospital should be immediate Modern operative treatment gives excellent results in early and acute traumatic cases, often necessitating a stay in hospital of no longer than three weeks Delay makes the prognosis much worse

REFERENCES

Carnitz, H (1929) *Acta chir scand* 65, 82
Hall, J B (1957) *J Bone Jt Surg* 39B, 659
Wilson, P D (1938) *ibid* 20, 379

THE SYNDROME OF THE SUSPENDED HEART

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THE occasional finding of abnormal electrocardiograms in patients without manifest cardiac disease may cause much difficulty in assessment of these subjects Without necropsy evidence of a strictly normal myocardium one cannot with assurance state that the electrocardiographic disturbance is not associated with heart-disease However, Evans and Lloyd-Thomas (1957) have, under the title of "The syndrome of the suspended heart," presented convincing evidence of the association of certain specific electrocardiographic "abnormalities" with a particular radiological configuration of the heart. Briefly, the electrocardiograms show abnormal S-T segments and T waves suggesting infarction of the lateral and postero-inferior portions of the left ventricle, or of left ventricular strain without abnormal voltages Radiological examination shows a heart that, during deep inspiration, appears to be suspended between the vascular pedicle above and the inferior vena cava below

We report here three cases of this syndrome seen by us in private practice since the publication of the article by Evans and Lloyd-Thomas (1957)

Case-reports

Case 1.—A girl, aged 12 years, was referred because of persistent headaches and abdominal pain, with failure to gain weight steadily Her past history was insignificant

On examination she was of ectomorphic build and 4 ft 11 in tall and weighed 67 lb Her blood-pressure was 110 60 mm. Hg and cardiac impulse normal A grade I early systolic murmur was present at the apex and along the left parasternal area A third heart sound was heard at the apex The remainder of the physical examination was irrelevant The urine contained albumin, but repeated examinations showed orthostatic albuminuria A full blood count and the erythrocyte-sedimentation rate were normal The urine contained no abnormalities on microscopy and was sterile on culture The blood-urea level was 20 mg per 100 ml A chest radiograph (fig 1) showed a long thin heart which, on deep inspiration, appeared to be lifted off the diaphragm and suspended by the vascular pedicle

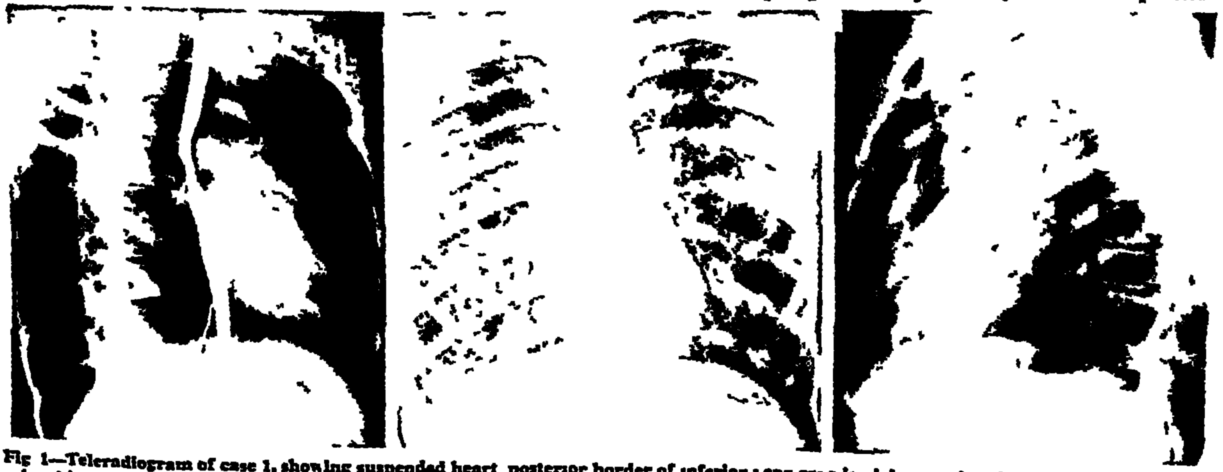

Fig 1—Teleradiogram of case 1, showing suspended heart, posterior border of inferior vena cava in right anterior oblique view is outlined in white

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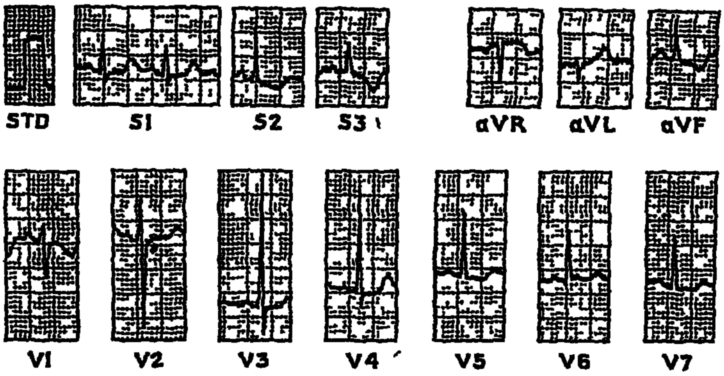

Fig 2—Electrocardiogram of case 1

and the inferior vena cava Electrocardiography showed depressed S-T segments in leads II, III, aVF, V5, V6, and V7, with inverted T waves in III and aVF (fig 2) V6 recorded one interspace higher showed smaller changes, and the abnormality was diminished but not obliterated by squatting The tracing was not altered by lying prone or by Valsalva's manœuvre

Case 2—A married woman, aged 24, had persistent gnawing pains under her left breast, unrelated to exertion She often felt breathless, both at rest and on exertion, and she tended to sigh frequently She was troubled by pins-and-needles in her hands Her past history was not significant

On examination she was of mesomorphic build and 5 ft 6$^1/_2$ in tall and weighed 141 lb She had congenital ichthyosis of the skin of the trunk and limbs Her blood-pressure was 120/70 mm Hg No abnormalities were detected in her heart or elsewhere Nothing abnormal was found in her urine Radiography of her chest (fig 3) showed a rather globular heart which, in the oblique views, rose high off the diaphragm during inspiration, throwing the inferior vena caval shadow into prominence Electrocardiography showed inverted T waves in leads II, III, aVF, V4, V5, V6 and CR4 (fig 4) These changes were less after effort The picture was not altered by sitting, lying prone, standing, squatting, or the Valsalva manœuvre Electrocardiography repeated two months later showed no change

Case 3—A man, aged 41, had been rejected for military service at the age of 18 because of possible rheumatic heart-disease In 1936, at the age of 20, he consulted a physician, but no clinical abnormality was found, although the electrocardiogram (fig 5) showed flattening of the T wave in lead II, and inversion of the T wave in lead III, with pronounced right axis deviation Since that time he has remained perfectly well and symptom-free Repeated physical examinations between 1955 and 1957 have shown no cardiac abnormalities A third heart sound and a grade-I systolic murmur were audible at the apex in 1955, but in 1957 the murmur was absent and the third sound was soft and inconstant These auscultatory findings were confirmed by phonocardiography

On examination he had a slightly depressed sternum, but the remainder of the physical examination was normal He was of mesomorphic build and 5 ft 7$^1/_2$ in tall and weighed 176 lb His blood pressure varied from 130 to 150 systolic and 80 to 90 diastolic A ballistocardiograph* in 1955 was interpreted as normal The electrocardiogram (fig 6), which has remained unchanged since 1955, revealed flattening of the T waves in lead II, with inversion in leads III, aVF, and V6 The degree of right axis deviation was much less than in 1936 The T-wave abnormality disappeared after effort or if the patient was placed in the sitting position with his legs horizontal Placing the electrode one interspace higher for V6 also produced a normal T wave The electrocardiogram was not altered by lying prone, standing, or the Valsalva manœuvre A chest radiograph (fig 7) showed a heart lifted well off the diaphragm, with prominence of the shadow of the inferior vena cava

Discussion

If the electrocardiograms discussed by Evans and Lloyd-Thomas (1957) are normal and associated with a peculiar stance of the heart within the thorax, it might be expected that the changes might be found even in children, as in the present case 1 The true incidence of this syndrome in a population cannot be known without mass surveys, but the recognition of the benign nature of the electrocardiographic findings is important, for the sake of reassurance of the patient and for the question of insurance

Case 2 indicates that the degree of electrocardiographic "abnormality" may be considerable However, the response to effort, as mentioned by Evans and Lloyd-Thomas (1957), helps to differentiate the changes from those due to coronary-artery disease

Evans and Lloyd-Thomas (1957) write:

> "The separation of the suspended heart from its close contiguity with its surrounding structures, particularly the diaphragm, disturbs the anatomical medium that customarily transmits the varying electrical potential generated by cardiac contraction, and this we consider gives rise to changes associated with this characteristic cardiogram"

If their theory is correct, it is to be expected that, in some cases, posturing of the patient might alter the anatomical relationship of the heart to its environs In

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* Bowen's ballistocardiogram (Smith-Perls model)

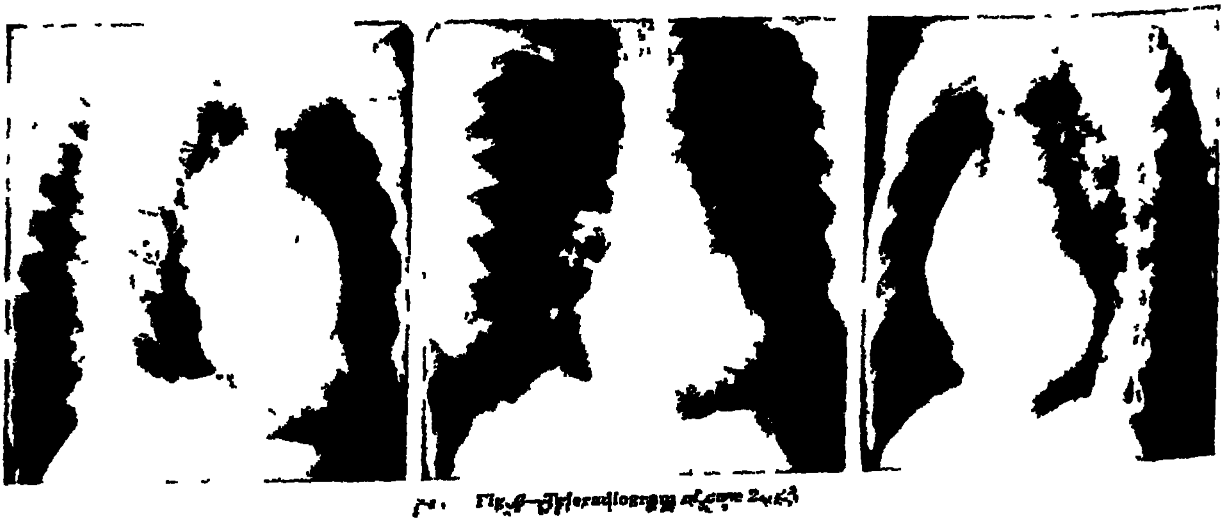

Fig 3—Teleradiogram of case 2

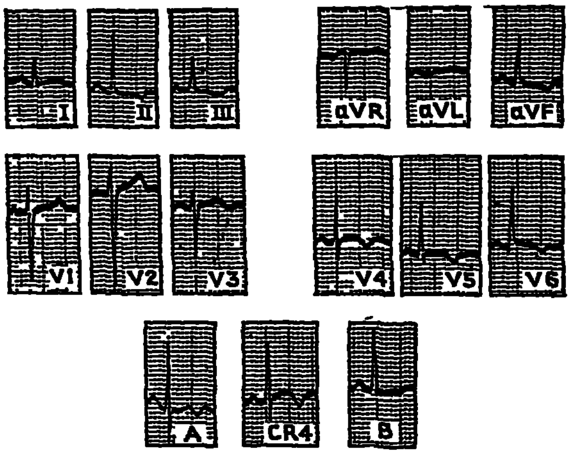

Fig 4—Electrocardiogram of case 2 A, CR4 recorded after effort, B, lead II recorded after effort

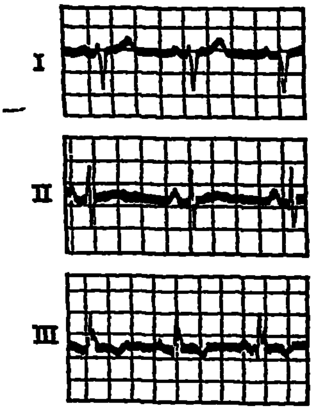

Fig 5—Electrocardiogram of case 3 in 1936

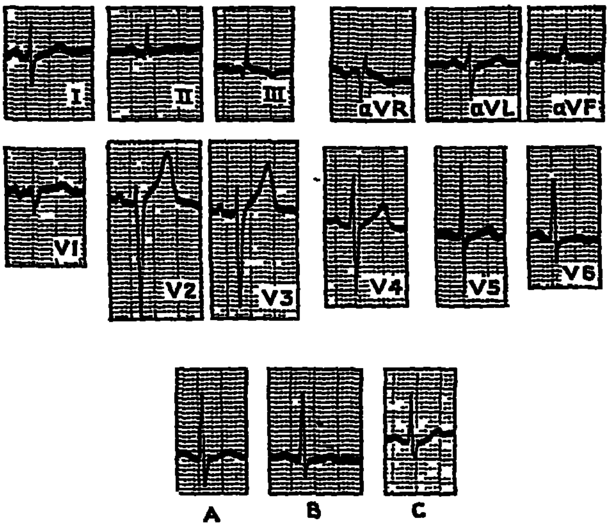

Fig 6—Electrocardiogram of case 3 A, V6 recorded with patient sitting, B, V6 recorded one intercostal space higher than normal, C, V6 recorded after effort.

case 3, with the patient in the sitting position with his legs horizontal, the T wave, previously inverted, became upright In case 1 squatting diminished the degree of abnormality

It therefore seems that the relationship of the heart to its environment, particularly the diaphragm, may be the factor concerned in causing the electrocardiographic "abnormality" Whether this is due to disturbance of the transmission of electrical potential, as stated by Evans and Lloyd-Thomas, or to an alteration of the direction of the repolarisation vector, as seems more probable to us, remains a matter for conjecture If an electrode could be placed directly on the heart in such a person, the mechanism might be further elucidated

As Evans and Lloyd-Thomas have done, we also have seen patients with similar radiological appearances of their hearts but with normal electrocardiograms We have not been able to confirm their observations that closer scrutiny of these radiographs shows more of the heart shadow in contact with the diaphragm than in those subjects with the "abnormal" electrocardiograms However, we do not deny the possibility that, in those with normal electrocardiograms, the anatomical relationships of the heart may be different from those of persons with the "abnormal" electrocardiograms discussed above

Summary and Conclusions

Three further cases of the "syndrome of the suspended heart", as described by Evans and Lloyd-Thomas (1957), are reported, one being in a child aged 12 years There is an association of a characteristic radiological picture of a heart lifted off the diaphragm and suspended between the vascular pedicle and the inferior vena cava, with an electrocardiogram showing S-T and T changes in posterolateral leads The benign nature of the syndrome is confirmed, and the abnormal changes are demonstrated in unipolar chest leads, in contrast to the bipolar chest leads used by Evans and Lloyd-Thomas

We thank Dr M M Suzman for the loan of the electrocardiogram of 1936 in case 3, and Mr A M Shevitz for the reproductions of the radiographs and electrocardiograms

REFERENCE

Evans, W, Lloyd-Thomas, H G (1957) *Brit Heart J* 19, 153

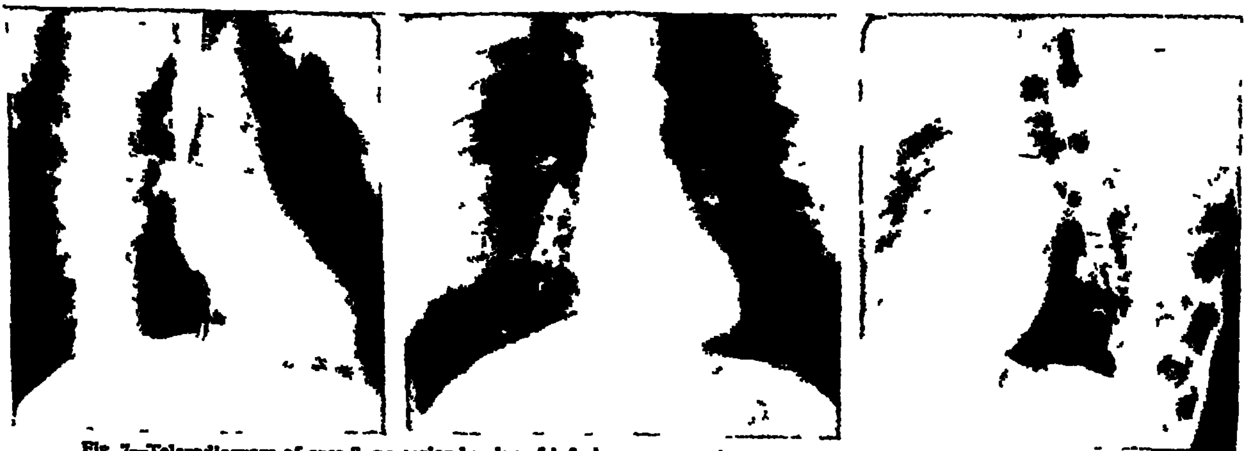

Fig 7—Teleradiogram of case 3 posterior border of inferior vena cava in right anterior oblique view is outlined in white

POSTOPERATIVE MALABSORPTION
SECONDARY PROTEIN MALNUTRITION SYNDROME

Z A Leitner
M D Berlin, L R C P E

The considerable literature on the malabsorption syndrome has been competently reviewed by Adlersberg (1957) and Volwiler (1957) in the United States, and different aspects of postoperative malabsorption have been discussed by Brain (1951, 1953, 1954), Welbourn and Doggart (1956), and Welbourn et al (1956) in this country The greater part of the relevant literature deals with steatorrhœa, electrolytes, hæmatological or vitamin deficiencies, and osseous changes There are few references to the malabsorption of proteins

A patient with " intractable avitaminosis " in a London hospital proved to have postoperative nutritional failure (protein malnutrition, secondary kwashiorkor) As I could not find a single similar published case I circulated the case-history widely, only to be informed that no such condition has ever been seen in a number of large gastroenterological departments (Dr W I Card, Dr F Avery Jones, Mr Rodney Smith, and Mr N C Tanner, personal communications) However, scrutinising Mr Rupert Corbett's postoperative material I found another patient in London who showed repeatedly the fully developed syndrome of protein malnutrition Publication of these cases may lead to the recognition and study of others

Case-reports

THE FIRST CASE

This was demonstrated briefly at a meeting of the Nutrition Society last December (Leitner 1958)

A man, aged 61, was admitted to a London Hospital in July, 1953, with four days' history of upper abdominal pain radiating into his left shoulder and arm, vomiting, and severe jaundice His serum-bilirubin level was 10 mg per 100 ml, thymol turbidity 2 units, alkaline-phosphatase 120 King-Armstrong units, Hb 13 5 g per 100 ml, and white cells 22,400 per c mm (polymorphs 84%) At operation on Aug 6, 1953, a hard mass felt in the head of his pancreas was thought to be a carcinoma, but histological examination later showed only chronic pancreatitis A partial gastrectomy was done, with resection of the head of the pancreas and choledochoenterostomy with insertion of the pancreatic duct into the duodenum After operation he temporarily lost weight

Course of Illness

June, 1955—He felt ill and was admitted for reassessment The findings were Hb 12 1 g, all pancreatic enzymes absent, total fæcal fat 36 3 g per 100 g of dried fæces, serum-protein 4 7 g per 100 ml (albumin 2 5 g, globulin 2 2 g) A high-protein low-fat diet was given, with large doses of pancreatin, vitamins, and iron, and after four weeks the patient was discharged greatly improved, with serum-protein 5 8 g per 100 ml

January, 1956—Readmitted He was passing three or four bulky motions daily, had lost weight, and had swelling and ulceration of his legs The findings were Hb 12 2 g, blood-sugar 102 mg per 100 ml, serum-proteins 4 3 g, serum-bilirubin 0 9 g, thymol turbidity 4 units, and alkaline phosphatase 18 units A high-protein low-fat diet was again given, with pancreatin, iron, and vitamins, and three weeks later his condition improved and he was discharged

May, 1956—Readmitted complaining of severe pain in his legs and of general malaise, he had œdema of his ankles, punctate pink spots with petechial striæ across his ankles and lower legs, and shallow trophic ulcers scattered all over his body, but mainly on his face and head It was then thought that he was having neither sufficient nor the right type of care and diet at home In hospital the purpuric striæ had spread up his legs to his thighs and rump, and a brown pigmentation, which appeared first on his legs, extended towards his trunk Meanwhile the purpuric staining had involved the whole of his trunk and become more noticeable in the pressure areas He had no bleeding from his gums Large doses of vitamins were given orally, and parenterally, but the skin eruption, which was thought to be due to a deficiency of vitamins B and C, further exfoliated

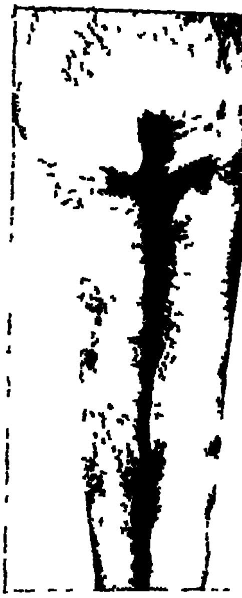

Fig 1—Mosaic-like crazy pavement dermatosis, with dry wrinkled xerotic skin between lesions and cracks in hyperpigmented areas

May 19, 1956—Hb 11 1 g per 100 ml, serum-proteins 3 5 g per 100 ml (albumin 1 3 g, globulin 2 2 g per 100 ml)

May 25, 1956—Blood-sugar tolerance fasting 93 mg per 100 ml, half-hourly figures 119, 150, 190, 193, 170 mg per 100 ml, with some excretion of sugar shown in the last two specimens

June 21, 1956—Serum-proteins 3 8 g (albumin 1 8 g, globulin 2 0 g)

Aug 3, 1956—Serum-proteins 3 6 g (albumin 1 5 g, globulin 2 1 g)

Aug 8, 1956—Intravenous ascorbic-acid test yielded in the urine only 21 mg of the expected 200 mg, blood-pyruvic acid 3 4 mg per 100 ml (normal values 0 1–1 0 mg, in marked thiamine deficiency up to 2 0 or 3 0 mg) 4 pints of plasma, followed by a litre of hydrolysed protein, together with massive doses of vitamin-B complex and vitamin C, was administered subsequently There was transitory improvement (on Aug 13 the serum-protein level was 5 2 g), but the patient relapsed within a week, and new pink spots and striæ and new ulcers appeared

Aug 22, 1956—I saw the patient in consultation at the hospital He was apathetic, wasted, and obviously ill, with moderate œdema of his ankles and sacrum, and answered questions mechanically I found no abnormality apart from sluggish tendon-reflexes Extensive pigmented pellagra-like dermatosis covered the greater part of his body, but places exposed to light were free from such lesions The skin in

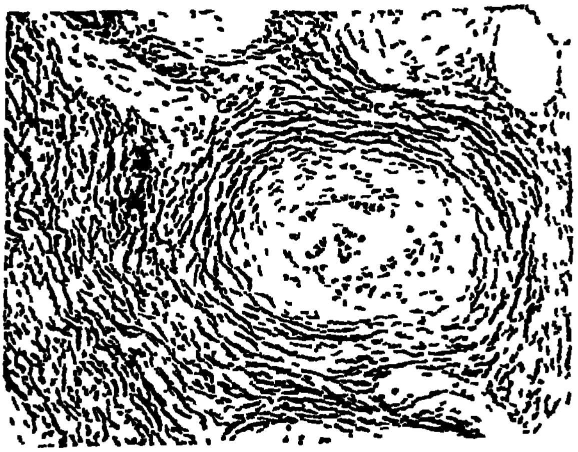

Fig 2—Dilatation of pancreatic duct, with severe periductal fibrosis, fibrous replacement of parenchyma and complete absence of acinar tissue (× 130)

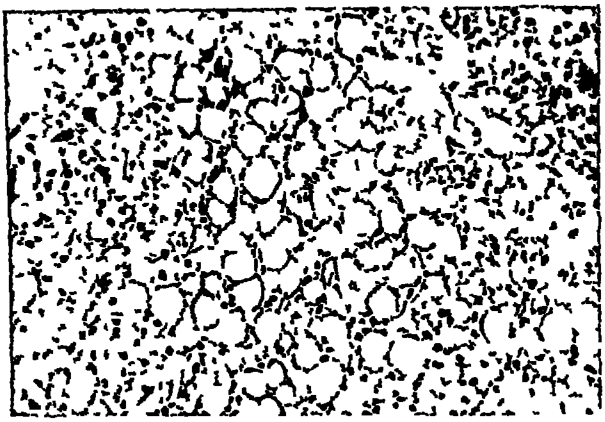

Fig 3—Very severe fatty change in liver (× 90)

between the lesions was dry, wrinkled, and in places scaly and xerotic, with exfoliation, giving the general impression of crazy-pavement or mosaic-like dermatosis There were numerous cracks, mainly in the hyperpigmented areas (fig 1) Scattered all over, but mainly on his legs and back, were punctate purpura-like spots and striæ, with pinkish pigmentation, at first sight similar to, but on examination quite different from, the perifollicular hæmorrhages of scurvy No changes were found in the mucosæ, mucocutaneous junctions, or conjunctivæ A sample of blood contained carotenoids 5 I U , vitamin A 56 I U , and vitamin E 0 14 mg per 100 ml

Aug 29, 1956—Prothrombin time 20 sec (normal control 15 sec), serum-calcium 8 6 mg per 100 ml , inorganic phosphorus 4 2 mg per 100 ml

Sept 6, 1956—Serum-proteins 3 8 g per 100 ml (albumin 2 1 g , globulin 1 7 g) Hb fell to 9 5 g He died on Sept 9

Necropsy

Brain œdema of white matter, slight atheroma of arteries at base *Heart* brown atrophy of myocardium *Vessels* slight atheroma of coronary arteries and aorta *Lungs* serous pleural effusions, 2 pints *Peritoneum* serous ascites 1 pint *Liver* very severe fatty change (floats in water), gallbladder distended and lined by smooth grey mucosa, old anastomosis between common bileduct and duodenum, with dilatation of common bileduct *Stomach* pyloric portion resected, old gastrojejunal anastomosis (intact), duodenal stump intact, adhesions between loops of upper jejunum in right hypochondrium but no evidence of side-to-side anastomosis *Pancreas* head removed, fibrosis of remaining body and tail, with dilatation of pancreatic duct (containing mucus), no communication between pancreatic duct and duodenum *Spleen* congested *Kidneys* cloudy swelling *Suprarenals* atrophied lipoid layer in cortex. *Bone-marrow* pink hæmopoietic marrow (floats) in neck and upper third of femoral shaft *Analysis of the liver* showed a fat content of 32 4% and vitamin-A content of 120 I U per g of fixed liver

Histological Report

Pancreas hypertrophy of islet tissue, complete atrophy of parenchyma, with chronic inflammation and fibrous replacement, and gross dilatation of duct (fig 2) Slight chronic inflammation and fibrosis of portal tracts of liver with proliferation of bile canaliculi and extreme fatty change (fig 3) Chronic inflammation of gastric mucosa Severe congestion and chronic inflammation of spleen Congestion, cloudy swelling, and ischæmic changes in *kidney* Atrophy of *epidermis*, with scattered focal deposits of blood pigment in fibrotic dermis of skin from medial side of left leg Focal atrophy of voluntary muscle-fibres and endoneural fibrosis of small nerve-bundles in dermis and subcutaneous tissue

THE SECOND CASE

A married woman, aged 59, was admitted to St Bartholomew's Hospital on Aug 31, 1950, having lost 2–3 st of weight during the preceding year, and developed anorexia, vomiting, and malaise, just before admission she became jaundiced In hospital a complete duodenal obstruction developed On Sept 5 pancreatico-duodenectomy (gastrojejunostomy, cholecystogastrostomy, resection of the head of the pancreas) was performed, and a large neoplasm was removed which completely filled the second part of the duodenum, encircling the common duct and papilla The growth was of primary duodenal origin, the head of the pancreas and the lymph-nodes not being infiltrated Recovery was uneventful, and she was discharged on Nov 1 on pancreatin and iron

First Readmission (Jan 28, 1952)

After being well for about a year, she developed steatorrhœa and lost weight in spite of her large appetite Her face was puffy, and œdema extended almost to both knees She had dry exfoliative dermatitis, a smooth red tongue, cheilosis, and angular stomatitis Her serum-protein level was 3 8 g per 100 ml (albumin 2 0 g , globulin 1 8 g) Her fæces contained fat-globules and undigested muscle-fibres Total fæcal fat 45 1% (10 8% unsplit) Hb 12 4 g per 100 ml White cells 4700 per c mm (differential count normal) Nitrogen balance negative over four days (5 3 g of N excreted daily) Of an average daily intake of 46 g fat (four days) she excreted 26 g in the stools She was given protein-rich fat-poor diet with 'Casydrol', 30 g of proteolised liver extract daily, and vitamin-B complex parenterally Feb 22 total proteins 3 8 g (albumin 1 8 g , globulin 2 0 g) March 5 total proteins 4 2 g (albumin and globulin each 2 1 g), œdema was still present, therefore 100 g of predigested protein ('Pronutrin') was given daily March 13 total proteins 5 1 g (albumin 2 8 g , globulin 2 3 g) March 28 total proteins 6 7 g (albumin 3 4 g , globulin 3 3 g) She was discharged on March 28, 1952, clinically recovered She had normal formed stools Her œdema and exfoliative dermatitis had disappeared

Second Readmission (Jan 30, 1953)

During the last two months increasing flatulence, anorexia, sweating of her face and neck when eating "she went to pieces" Pain radiated into her left shoulder and axilla Puffiness of the face, gross swelling of her legs, considerable sacral œdema, Smooth red denuded tongue in spite of injections of vitamin-B complex by her doctor, bilateral pleural effusion, generalised osteoporosis Hb 11 8 g , white cells 8000 (differential count normal) Total serum-proteins 3 2 g (albumin 1 7 g , globulin 1 5 g) Treatment high-protein low-fat diet, vitamins, iron, pancreatin, daily infusion of 25 g of dried serum-albumin in 5% glucose Feb 20 total proteins 5 1 g (albumin 2 8 g , globulin 2 3 g) Feb 25 total proteins 5 8 g (albumin 3 05 g , globulin 2 75 g), pyruvic-acid-tolerance curve normal (fasting 0 75 mg of pyruvic acid per 100 ml , 1 34 mg per 100 ml 1 hour after 50 g of glucose) Feb 27 discharged feeling well, œdema and pleural effusion had disappeared

Follow-up

During 1953–57 the patient was regularly followed up by Mr Corbett with the assistance of Dr E F Scowen She ate, felt and looked well, and kept her weight steady Hb on Oct 5, 1956, was 15 4 g I examined her with Mr Corbett on May 24, 1957 Clinically she was well Total proteins were 6 0 g (albumin 4 0 g , globulin 2 0 g), Hb 14 2 g She reported that every day she ate a meat or a fish meal, usually one or two eggs, and a pint of milk reinforced with casylan She had taken pancreatin continuously and had intermittent courses of vitamin-B complex In spite of this she had occasionally a smooth tongue, with mild cheilosis and angular stomatitis

Third Readmission

On Sept 18, 1957, she was readmitted under Dr Scowen She felt well, apart from sweating of her face after eating, but had become worried about herself On clinical examination nothing abnormal was found Investigations showed blood-pressure 135/80 mm Hg, Hb 14 5 g per 100 ml , mean corpuscular volume 84 cμ , blood-urea 32 mg per 100 ml , serum-proteins 5 3 g per 100 ml (albumin 3 5 g , globulin 1 8 g), with normal electrophoretic pattern, thymol turbidity 3 units, total serum-bilirubin 0 5 mg per 100 ml , direct negative, serum sodium 141, potassium 5, chlorides 111, alkaline reserve 25 mEq per litre, serum-calcium 8 8 mg per 100 ml , inorganic phosphorus 3 7 mg per 100 ml , alkaline phosphatase 12 King-Armstrong units Glucose-tolerance test fasting 118, half-hourly figures 205, 220, 162, 128, 136, and 118 mg per 100 ml Fæces undigested muscle-fibres and fatty-acid crystals, total fat 30% of the dry matter Radiography lungs normal, spine, pelvis, and hands showed diffuse osteoporosis

Discussion

In case 1 the provisional diagnosis of an intractable vitamin-deficiency state was supported by the symptoms and signs and the biochemical data My colleague, Dr T Moore, commenting on the exceedingly low level of carotenoids and vitamin E, reminded me of his similar findings in kwashiorkor (Trowell et al 1954a and b) Brock (1955) also has emphasised that the clinical appearances of kwashiorkor may be modified by the complicating deficiencies of vitamins During the consultation in case 1 the diagnosis of severe avitaminosis was extended to that of nutritional failure, and it soon became evident that the main underlying cause was protein malnutrition Although, because of the patient's death, further investigations could not be made, the diagnosis was confirmed by the low serum-protein level (3 8 g per 100 ml or less) which persisted for several months with inverted albumin/globulin ratio, and subsequently by the necropsy findings These serum-protein levels, like those in case 2 during the first and second readmissions (3 8 and 3 2 g per 100 ml respectively), were substantially lower than those published in large series of kwashiorkor (Dean and Schwartz 1953, Kinnear and Pretorius 1956)

Dermatological lesions are not obligatory signs of protein malnutrition but they do develop in different parts of the world in 25–80% of the cases, and then they always appear on parts of the body not exposed to light Dryness, scaling, and wrinkling of the skin are always present, often with xerosis and pigmentation, with or without mosaic, crazy-pavement, or enamel-paint-like dermatosis According to Gopalan (1955) in India it often starts with pinkish punctate discoloration, mainly on the anterolateral aspect of the legs, as in case 1 This has also been observed in Kampala and other places (Trowell et al 1954a) Although, sometimes a prolongation of the prothrombin-time has been reported in association with these punctate purpura-like spots, neither in case 1 nor in the cases described in Tunis (Caruana et al 1953) was the prothrombin-time prolonged In the Tunisian cases the red spots could not be prevented by treatment with vitamin C and vitamin K

In protein malnutrition the skin lesions always quickly disappear on a high-protein diet, as in case 2 during the first readmission, but neither diet nor plasma infusions had the slightest influence on the exfoliative dermatosis extending over two-thirds of the body's surface in case 1 The serum-protein levels were lower and the clinical symptoms and signs were much more severe in case 2 during the second readmission In spite of this no dermatological lesions developed as on admission a year earlier

The protein-malnutrition syndrome is much less common in adults than in children (Trowell et al 1954a), and the extent and the severity of the skin lesions seem to bear no direct relation to the severity of the disease (Rao 1955) Signs of the syndrome, with typical though limited dermatosis, were described in two Polish refugee women, aged 25 and 40, who suffered great privations during migration through Russia and the Middle East until they reached Uganda (Brown and Trowell 1944), but I am aware only of two other cases of this syndrome ever described in a white man A Dutch seaman recovered completely on treatment for a year with pancreatin, choline, and a protein-rich diet (Van Steenis 1950) A South African male, aged 40, was dramatically cured after correction of a 6 ft blind loop surgically constructed 3 ft proximal to the ileocæcal valve (Kritzler and Schrire 1958)

It was impressive how quickly the clinical condition and the serum-protein level reacted in both patients (in case 1 only during the first two readmissions) to simple dietetic measures reinforced by pancreatin and vitamins Unfortunately we have so far no means of defining protein malnutrition exactly, because we cannot estimate the protein content of the body or assess even approximately the extent of the body's stores of protein We therefore had to be satisfied with estimating the total serum-proteins, and this, together with the estimation of the protein fractions, seemed to be a surprisingly accurate guide so far as the fluctuation of the clinical condition was concerned This was recently emphasised also by Waterlow (1956) We found, however, some difficulty in explaining the comparatively sudden fall and sudden rise of serum-protein levels Both these patients made a spectacular recovery within three to eight weeks with the help of only dietetic measures during their first readmission Thus the serum-protein level in case 1 rose from 4 7 to 5 8 g per 100 ml and in case 2 from 3 8 to 6 7 g per 100 ml It therefore appears that the low serum-protein levels were due in both cases to comparatively sudden onset of malabsorption

Increased fæcal excretion of fat (Gordon-Taylor et al 1929) and considerable loss of weight (Maclean et al 1954) have been known for some time to follow gastric operations, even when the secretion of pancreatic enzymes is normal Resection of the head of the pancreas, on the other hand, leads to excessive loss of both fat and nitrogen in the fæces (Wollaeger et al 1948, Nicolaysen and Ragaard 1955) Increased excretion of fat and nitrogen in proportion to the pancreatic damage was found also in patients with chronic relapsing pancreatitis (Dornberger et al 1948) Pancreatic enzymes were absent in case 1, but this did not prevent a rise in the serum-protein level within a few weeks from 4 7 to 5 8 g per 100 ml Although at times high-protein diet and intravenous infusion of comparatively small amounts of albumin seemed to restore quickly the malabsorption defect (second readmission of case 2), at other times large parenteral infusions of plasma yielded at best an improvement for only a few days, followed by death (case 1, third readmission)

During the siege of Budapest Véghelyi (1948) noticed that babies fed on a diet poor in animal proteins developed gross œdema and severe fatty infiltration of the liver following decrease in pancreatic secretion The development of pancreatic failure took only one or two weeks, the younger the child the quicker was the failure The whole process could be reversed within a few days if enough milk or methionine was given It was much harder to reverse, or became irreversible, if treatment started later in the illness The macroscopic appearance of the pancreas was in these cases almost normal, but microscopy showed small shrunken acinar cells, with depletion of the cytoplasm and disappearance of the zymogen granules, fibrosis, and scarring By experimental feeding similar changes were produced in rats, and the excretory changes in the pancreas preceded fatty infiltration of the liver Davies (1948) described the atrophy of the acinar cells in the pancreas, with a diminution in the numbers of secretory granules, gross fibrosis, and dilatation of the ducts, as the fundamental lesion in kwashiorkor, which was necessarily followed by extensive fatty infiltration of the liver " In a man of 24 the pancreas had been almost completely superseded by fibrous tissue ", a description very similar to our case 1

Friedman and Friedman (1946), by giving a protein-poor diet to rats, produced a loss of cytoplasm in the acinar cells of the pancreas until only a thin rim remained round the vesicular nucleus Fatty infiltration of the liver was present in all the rats Similar changes were produced by giving ethionine (an antagonist of methionine), the lesions could be prevented by previous administration of methionine but not cystein or glucose, both of which usually prevent fatty infiltration of the liver (Farber and Popper 1950) Moreover the pancreas produces more enzymes on a diet high in complete proteins (containing all essential aminoacids) than on a diet that is either low in proteins or does not contain complete proteins—e g , gelatin and zein (Magee and Anderson 1955)

From these experiments it appears that the normal structure and function of the pancreas depend greatly on an adequate supply of complete proteins The experiments are also in agreement with the clinical, experimental, and pathological work of Davies (1948) and Veghelyi (1948) and with newer findings that severe atrophy of the acinar cells, with fibrosis of the pancreas of whatever ætiology, produces necessarily an extensive fatty infiltration of the liver (Bras et al 1956) Furthermore Veghelyi et al (1950) have shown that, in early cases, an adequate supply of proteins was followed within ten days by clinical improvement and by a rise in the serum-protein level, improvement, if any, in more chronic cases took much longer This observation is borne out by my own experiences both patients reported here improved quickly after being given a high-protein diet during their first readmission The serum-protein level in case 2 rose during the second readmission from 3 2 to 5 8 g per 100 ml within three weeks on a high-protein diet and intravenous dried serum-albumin 25 g daily, and coincidentally the gross generalised œdema and bilateral pleural effusion disappeared completely, and no further relapse occurred during the subsequent five years In case 1, however, where the readmissions occurred only at a more severe stage of the disease, recovery was impossible

In the two cases here recorded this postoperative malabsorption state led to the typical syndrome of secondary protein malnutrition All the evidence suggests that the pancreas, the organ with the greatest protein turnover in the body, has a key position in the development of the protein-malnutrition syndrome It appears that the vicious circle leading to the more severe stages of protein malnutrition and eventually to death might be arrested nearly at any stage—e g , fatty infiltration of the liver, and partial pancreatic fibrosis—provided that structural changes are still reversible, but, when extensive shrinking of the acinar tissue, with gross atrophy of the parenchyma of the pancreas and massive fibrous replacement and scarring, has taken place, interrupting communication between pancreas and duodenum, as in case 1, no reversion is possible

Summary

Two patients are reported who developed a syndrome of protein malnutrition, hitherto undescribed, some years after pancreaticoduodenectomy

The possible mechanism of the malabsorption leading to secondary protein malnutrition is discussed

My thanks are due to Dr T St M Norris and Mr Rupert Corbett for asking me to see cases 1 and 2 respectively, for much advice, and for permission to publish, to Dr T Moore, Dr I M Sharman, and Dr E Montuschi for their help, and to many colleagues in this country and overseas who discussed several aspects of protein malnutrition with me, particularly Prof J F Brock, Prof J N P Davies, Prof Kenneth Hill, and Prof B S Platt, and Dr W I Card, Dr H C Trowell, Dr J C Waterlow, and Dr Cicely Williams

REFERENCES

Adlersberg D (1957) A Mount Sinai Hospital Monograph on the Malabsorption Syndrome New York
Brain, R H F (1951) *Lancet*, i, 1137
— (1953) *Proc R Soc Med* 46, 438
— (1954) *ibid* 47, 987
Bras G , Waterlow, J C , Depass E. (1956) *J trop Pediat* 2, 147
Brock, J F (1955) *Voeding*, 16 99
Brown, J S , Trowell, H C. (1944) *Lancet*, ii, 812.
Caruana M , Hamza B Ghitels, H (1953) *Tunis méd* 41, 265
Davies J N P (1948) *Lancet*, i 317
Dean R F A , Schwartz, R (1953) *Brit J Nutr* 7, 131
Dornberger, G R , Comfort, M W , Wollaeger, E E , Power, M H. (1948) *Gastroenterology*, 11, 691

References continued at foot of next column

“FALSE” SICKLE CELLS

UNDER THE POLARISING MICROSCOPE

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SICKLE-CELL trait and sickle-cell anæmia can be distinguished from one another by examining fresh preparations of the venous blood under anaerobic conditions (Sherman 1940) In persons with the trait less than 1% of the erythrocytes are sickled, whereas in sickle-cell anæmia the proportion is 30–60%

During research in the Petromagoula area, where sickle-cell anæmia and trait are prevalent (Choremis et al 1953, 1957), 37 members of the families of 12 patients were found to have the trait In fresh preparations of their venous blood, with added sodium metabisulphite, sickle cells appeared after six to twelve hours' incubation, a holly-leaf form being predominant (fig 1)

Silvestroni and Bianco (1946) in Italy, noted differences in the sickling between patients and carriers of the trait In the carriers the sickling took longer to appear (sometimes twenty to twenty-four hours) Only a small proportion of the cells assumed the holly-leaf form

Sturgeon et al (1955) described in sickle-cell-D disease a slow and limited sickling, with holly-leaf forms predominant, whereas in sickle-cell anæmia sickling was rapid and complete

In 1952 we observed in healthy persons a slow sickling limited to a small proportion of red cells, but this was subsequently held to be false (Caminopetros 1952, Choremis et al 1953, Lie-Injo Luan Eng 1953) Our sickle cells were ascribed to external stresses—notably, long incubation In general, sickling of cells after more than twelve hours' incubation, even where it is complete, is taken as false Thus, in the Kakwa tribe the sickle-cell incidence rose from 12% to 25% when the preparations were left overnight (Lehmann and Raper 1949), and this increase was attributed to the appearance of false sickle cells On the other hand it is difficult to see why

DR LEITNER REFERENCES—*continued*

Farber, E , Popper, H (1950) *Proc Soc exp Biol , N Y*, 74, 838
Friedman, S M , Friedman, C L (1946) *Canad Med Ass J* 55, 15
Gopalan, C (1955) in Protein Malnutrition (edited by J C Waterlow), p 162 Cambridge
Gordon-Taylor, G , Hudson, R V , Dodds, E C , Warner, J L , Whitby, L E H (1929) *Brit J Surg* 16, 641
Kinnear, A A , Pretorius, P J (1956) *Brit med J* i, 1528
Kinkler, D M , Schnure, V (1958) *Lancet*, i, 510
Leitner, Z A (1958) *Proc Nutr Soc* 17 ix
Maclean, L D , Perry, J F Kelly, W D , Mosser, D G , Mannick, E , Wangensteen, O H (1954) *Surgery*, 35, 705
Magee, D F , Anderson, E G (1955) *Amer J Physiol* 181, 79
Nicolaysen R , Ragnard, R (1955) *Scand J clin Lab Invest* 7, 271
Rao, M V R (1955) *in* Protein Malnutrition (edited by J C. Waterlow), p 219 Cambridge
Trowell, H C , Davies, J N P , Dean, R. F A (1954a) Kwashiorkor London
— Moore T , Sharman, I M (1954b) *Ann N Y Acad Sci* 57, 734
Van Steenis, P B (1950) *Docum neerl indones Morb trop* 2, 44
Véghelyi, P V (1948) *Lancet*, i, 497
— Kemeny, T T , Pozsonyi, J , Sos, J (1950) *Amer J Dis Child* 79, 65, 658
Volwiler, W (1957) *Amer J Med* 23, 250
Waterlow, J C (1956) *W Indian med J* 5, 167
Welbourn R B , Doggart, J R (1956) *Brit J Surg* 44, 320
— Nelson, M G , Zacharias, F J (1956) *ibid* 43, 422
Wollaeger, E E , Comfort M W , Clagett, O T , Osterberg, A E (1948) *J Amer med Ass* 137, 838

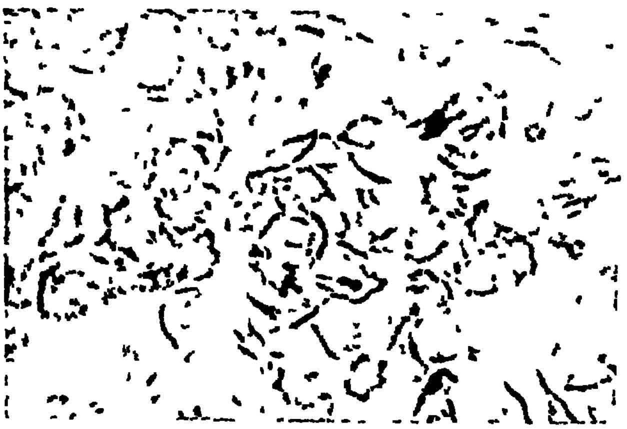


Fig 1—Sickle-cell trait Moderate sickling Predominance of holly-leaf forms. (×550)

“false” sickling has so far been observed only in peoples who exhibit the trait, and not in the blood of Europeans, in whom it is absent

Since 1952 we have seen 106 new cases of the limited form of sickling (fig 2) Of the people showing it, some come from the Greek mainland or islands, while others are Greek and Armenian refugees from Asia Minor or gipsy settlers in Greece Some of them—not always related to patients with anæmia—have signs of the trait such as target cells, and increased resistance of red cells Nevertheless it was still necessary to prove the existence of S hæmoglobin in these cases, since this is thought to be the agent responsible for sickling (Pauling et al 1949)

The characteristic optical property of S hæmoglobin, either in sickle-cells or in its solutions is birefringence, and this is seen under the polarising microscope (Sherman 1940, Perutz and Mitchison 1950, Ascenzi and Silvestroni 1953) We decided to ascertain whether the so-called false sickle-cells were birefringent

Our examinations were made at the Institute of Geology with a ‘Panphot’ Ernst Leitz polarising microscope Its arc lamp provided the necessary high-intensity light The choice of objective (P6L 45 1) and eyepiece 12x were satisfactory

Blood from 73 of our 106 cases with slow and limited sickling was examined, on the first or second day of the appearance of *sickle-cells* Unlike the red cells of normal discoid form, all these cells exhibited definite birefringence (fig 3)

These findings point to the presence of S hæmoglobin Hence the sickling in these cases, though restricted and incomplete, must be due to intrinsic factors It is not an artefact

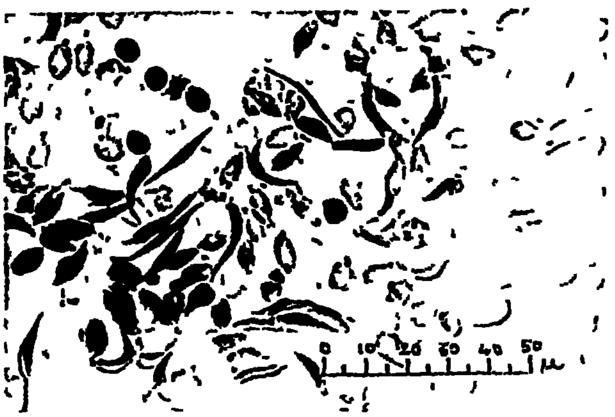


Fig 2—Slow and limited sickling after 8 hours incubation

We now think it probable that sickle-cell anæmia is caused by multiple genetic factors, and that the complete form of sickling may decline to minor forms, and eventually be extinguished

It is well established that in the sickle-cell trait the amount of S hæmoglobin ranges from 22% to 46% An exceptional case has been reported in which it was 5%, but the red cells could not be sickled The amount of S hæmoglobin in cases with slow and limited sickling will have to be determined We may note, however, that the abnormality of the red cells is not confined to the hæmoglobin but *extends to the cytoplasm and the cell* membrane (Perutz and Mitchison 1950, Ponder 1951)

Summary

In 73 cases showing the slow and limited sickling which was described in 1952 the sickled red cells have been examined under a polarising microscope They were found to be birefringent, as in cases of complete sickling

This finding supports the view that the sickling observed, though slow and limited, is genuine—not false, as has been suggested

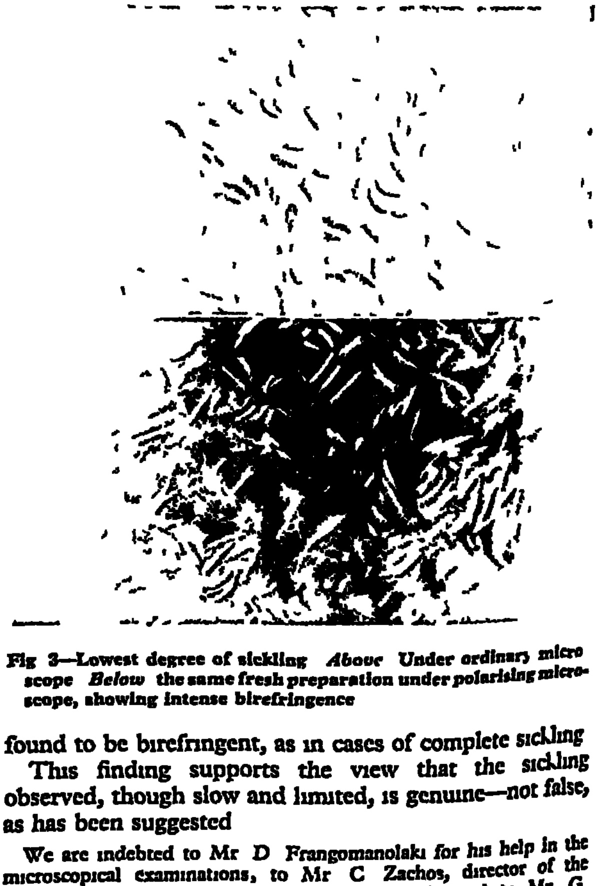


Fig 3—Lowest degree of sickling *Above* Under ordinary microscope *Below* the same fresh preparation under polarising microscope, showing intense birefringence

We are indebted to Mr D Frangomanolaki for his help in the microscopical examinations, to Mr C Zachos, director of the Institute of Geology and Subsurface Research, and to Mr G Marinos, chief of service of the institute

REFERENCES

Ascenzi, A, Silvestroni, E (1953) *Blood*, 7, 1061
Caminopetros, J (1952) *Lancet*, i, 687
Choremis C, Ikin, E W, Lehmann, H, Mourant, A E, Zannos, L (1953) *ibid* ii 909
— Zannos, L, Ikin, E W, Mourant, A E, Lehmann, H (1957) *ibid* ii, 1333
Lehmann, H, Raper A B (1949) *Nature, Lond* 164 494
Lie-Injo Luan Eng (1953) *Docum med geogr trop* 5, no 3, p 266
Pauling L, Itano, H A Singer, S J, Wells, I C (1949) *Science*, 110, 543
Perutz, M F Mitchison, J M (1950) *Nature, Lond* 166, 677
Ponder, E (1951) *C R Soc Biol Paris*, 145, 1665
Sherman, I J (1940) *Bull Johns Hopk Hosp* 67 309
Silvestroni, E, Bianco I (1946) *Haematologica* 29 455
Sturgeon, P, Itano, H A, Bergren, W R (1955) *Blood*, 10, 389

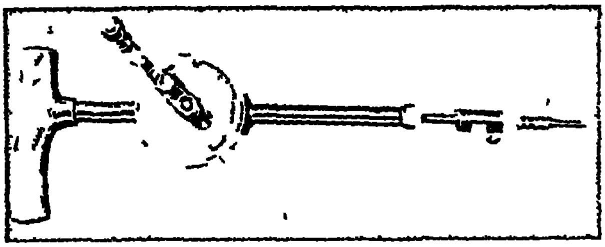
New Inventions

A NEEDLE TREPHINE

FOR the past three years I have used a needle trephine which can be readily made in any laboratory The trephine has been used both manually and with electrical power It has been employed in man and laboratory animals for placing surface electrodes, and deep cortical electrodes, emergent exploration of the subdural space and subarachnoid space, placing needle electrodes in the deep nuclei of the brain, and tapping the ventricular system for placing air and phenolsulphonphthalein solution for evaluation of the ventricular system

The trephine is made by taking a 16-gauge lumbar-puncture needle, and filing a groove in the hilt of the needle 90° from the original groove that receives the locking tongue of the stylet The stylet is then rotated 90° from its normal position and set into the prepared groove The needle with the stylet in place is then sawed at 45° angle 2 cm from where the hilt begins The opposite side of the needle and stylet are filed to a 45° angle from the horizontal Once this is done, the stylet is rotated again back to its normal, originally designed position which makes for a point with opposing 45° angles resulting in serrated or cutting edges

A small adapter was made out of brass which receives the hilt of the needle and is locked into place by a set screw The opposite end of the adapter has a straight shaft which can be fitted into a Jacob's chuck or into a locking twist drill chuck (see figure)



Twist drill, chuck adapter, and needle trephine

The obvious advantage of this needle trephine is that it perforates the skull without a surgical incision With the stylet of the needle trephine in its normal position, the scalp is perforated under local anaesthesia as a puncture Once the outer table of the skull is encountered, the stylet of the needle is turned into its cutting position of 180°, and the hilt of the needle is placed into the adapted chuck With a limited number of turns, the needle passes through the tables and the needle can be felt making its final break through the inner table The length of the needle precludes it going more than a few millimetres beyond the inner table If the needle trephine has been directed properly for the intended target, the smaller needle or the needle electrode can be taken and advanced through the trephine needle In the case of a ventriculogram, a no 20 smooth bevelled needle can be directed into the lateral ventricle If the line of flight of the needle trephine has not been properly directed, it is necessary to remove the needle trephine and to advance the smaller ventricular cannula or the smaller electrode needle in the proper direction, which is possible because these needles are small compared to the trephine needle, and their direction can be changed The puncture opening in the scalp is readily sealed with 'Aeroplast'

The needle trephine has all the disadvantages of the twist drill holes, but these disadvantages are outweighed by the simplicity when it is not desirable to display the brain surface I have not employed this drill in tumour biopsy, or to tap cerebral or suprasella cysts, but the instrument would lend itself well to these procedures With it I have placed over 100 trephine openings over various areas of the skull There has been no infection or hæmorrhage The procedure is not unduly painful to the patient

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Medical College of Georgia,
Augusta, U S A

GEORGE W SMITH
M D

Reviews of Books

Attempted Suicide

Its Social Significance and Effects E STENGEL, M D, M R C P, professor of psychiatry, University of Sheffield, NANCY G COOK, A M I A, psychiatric social worker Maudsley Monographs no 4 London Chapman & Hall, for the Institute of Psychiatry 1958 Pp 136 25s

SUICIDE is a subject of great psychiatric and sociological importance with many unsolved and even unexamined problems In 1952 Professor Stengel first pointed out that the environmental setting of attempted suicide and its repercussions on society had never been adequately investigated, partly because it was assumed that successful and unsuccessful suicides formed a homogeneous group He propounded a number of questions for future research, some results of which were summarised in 1956 and are presented in detail here He and his collaborators have studied " the relation of the individual to the social environment in the course of the suicidal attempt ", its " effects on the person's social relationships ", and " the reactions of the human environment and of society " in five groups totalling 630 patients admitted to hospital (three groups in observation wards, one in a psychiatric hospital, and one in a general hospital) and compared them with a series of suicides from a coroner's court Two of the groups followed up for as long as six years confirmed the clinical impression that only a minority finally succumbed to suicide They conclude that attempted and successful suicides should be regarded " as two different though overlapping populations " In contrast to suicide, " suicidal acts irrespective of psychiatric background " are " incidents in the course of struggle for adjustment social behaviour patterns " not " self-destructive " but " an alarm signal " or " appeal to the human environment "

This thesis is probably correct for a proportion of cases but applied to all seems an oversimplification on the authors' own evidence It does not explain the steep rise of suicidal attempts in the last decade—partly due to the easy availability of sedative drugs for minor psychiatric disturbances—at a time when social conditions and community care have steadily improved Nor can it explain suicidal attempts in response to hallucinations, delusions, the conviction of severe illness, fear of insanity, and insomnia, or following crimes of violence or suicide pacts, or in patients already living a sheltered community life, as in mental hospitals

The book makes difficult reading, partly because of its style The text is broken by 33 tables, not all helpful or readily comprehensible 44 representative case-histories, varying in length from 4 lines to almost a page, demonstrate that to obtain and present sound psychiatric case material is the chief difficulty in studies based on large numbers of patients

The Art of Clinical Refraction

T H WHITTINGTON, M D, M R C P, D O M S, ophthalmic physician, the Royal Eye Hospital, London London Oxford University Press 1958 Pp 294 30s

DR Whittington has succeeded in animating refractive work, and his readers will be stimulated by his zest and interesting presentation of clinical problems in a subject too often considered dull and dry Although refraction is a small part of ophthalmology it is a large part of routine practice for most ophthalmologists An intelligent appreciation of all the factors concerned in a patient's visual discomfort, and a conscientious application of the necessary subjective and objective tests, are essential for the relief of symptoms and reassurance of the patient

The book is practical and devoid of higher mathematics, and its value lies in the physician's approach to the art as well as the science of refraction Criticism concerns trifling errors Fig 57 (*a*) and (*b*), to illustrate the actions of the superior and inferior oblique muscles, are incorrectly drawn to meet the description in the text, and fig 54 (the Maddox rod test) would look better if all the vertical test results were set out in one row and the horizontal in the other "Spasmodic" is perhaps an inappropriate description for contractural torticollis (wry neck) of orthopædic interest

The author has put into the book much wisdom, the outcome of long clinical experience, enriched by the human interest he has taken in his patients It will therefore be of particular value to the young ophthalmologist—and indeed to many of maturer years

Enzymes

MALCOLM DIXON, SC D , F R S , reader in enzyme biochemistry in the University of Cambridge, fellow of King's College, Cambridge, EDWIN C WEBB, M A , PH D , lecturer in biochemistry in the University of Cambridge London Longmans, Green New York Academic Press 1958 Pp 782 90*s*

THIS is a scholarly and original book involving much of the authors' highly personal and critical approach to enzyme problems in addition to a comprehensive survey of the literature of known enzymes The subject is treated at a level suitable for research-workers and advanced students The book is mainly concerned with the elucidation of general principles underlying the nature, structure, mechanism of action, and kinetics of enzymes, and is only secondarily an account of the more functional aspects of the role of enzymes in metabolism In order to clear the ground for the very full treatment of basic principles, factual data concerning individual enzymes, including details of sources, substrates attacked, activators, and the chemical reactions catalysed, have been grouped together in encyclopædic tables Thus table V is a list of 659 enzymes occupying 42 pages arranged according to the reaction-type and thought to include, with literature references, all clearly identified enzymes described up to 1957 The classification follows that already brilliantly sketched in 1949 in Dr Dixon's small book *Multi-enzyme Systems* A valuable step forward in enzyme classification has undoubtedly been achieved This book is a highly valuable contribution to knowledge of and should become a standard work on the basic principles of enzymology

Laboratory Medicine Hematology

JOHN B MIALE, M D , professor of pathology, University of Miami School of Medicine, director of clinical pathology, Jackson Memorial Hospital, Miami, Florida London Henry Kimpton 1958 Pp 735 112*s* 6*d*

THIS is not a book for physicians, as the title is understood in this country, but for clinical pathologists, and really for those specialising in hæmatology The general clinical pathologist may find it useful as a reference book, for it is detailed, up-to-the-minute, and surprisingly complete But the effort to make it complete has involved the author in masses of detail that do not make easy reading or allow him to give clear indications for action Much of the information is helpfully gathered into tables, but, in a manner often seen in American texts, they give no indication about relative importance Thus, table 22 lists 34 chemicals that have caused methæmoglobinæmia, together with 6 other causes, including "ingestion of coloured wax crayons or chalk", table 67 lists 55 causes of eosinophilia—a remarkable feat, though few of the causes are important in practice A more valuable section lists 37 cases of interpretation of bone-marrow findings, giving brief details of the history, physical examination, and other pertinent laboratory findings together with a discussion of how all this material was put together in reaching a diagnosis This is indeed the stuff of medicine, but this method is not used in other sections It is hard to find any point in hæmatology that is not mentioned for example, the book includes the changes in the differential white-cell count from birth to 21 years, the laboratory findings in the hæmoglobinopathies, including Hb-I trait, and the recommended types of blood or blood product for transfusion in blood diseases

The bibliography is immense and all titles are given of papers listed The illustrations are mostly black-and white, but some are from colour photomicrographs, the reproduction of the colour photographs is not very good, Professor Miale knows well the diagnostic importance of clear nuclear detail in erythroblasts, but the pictures of *pronormoblast* and other normoblasts show featureless magenta blobs for nuclei The book will find its most popular use among the reference works in the clinical laboratory

Ulcerative Colitis

HARRY E BACON, B S , M D , SC D , LL D , F A C S , F A P S , *professor and head of department of proctology, Temple University, Philadelphia* Philadelphia J B Lippincott London *Pitman Medical Publishing Co 1958 Pp 395 120s*

Dr Bacon is well known to British proctologists not only through his many writings but as a man of thoroughness and energy A book from him, therefore, on the topical subject of ulcerative colitis is welcome—all the more so because only two other works are solely devoted to this subject This latest one is essentially factual in its approach and has the virtue of being comprehensive with but *few omissions of reference to relevant* work The ætiological hypotheses are presented fairly Surgical detail is contained only in the last half of the work, and earlier chapters contain much useful information, ranging from pathology, diagnosis, and complications to conservative therapy, including the use of steroids Appropriately a chapter on the effect of the disease on pregnancy and vice versa is included The book is illustrated profusely, and sometimes superfluously—*a pity, since the cost is high for a work on a subject with* limited appeal

External Collimation Detection of Intracranial Neoplasia with Unstable Nuclides

G M SHY, M D , M R C P , R B BRADLEY, B S , W B MATTHEWS, Jr , B S , department of health, education and welfare, Bethesda, U S A Edinburgh and London E & S Livingstone 1958 Pp 144 30*s*

THE title of this book reflects fairly its highly technical content and style of expression Injections into either the arteries leading to the brain or the cerebrospinal space to confirm the diagnosis of a cerebral tumour cause discomfort to the patient and carry certain hazards The *development of* alternative methods for detecting and localising tumours *within the skull is clearly important The authors* recount their experience in using radioactive isotopes, which may be concentrated in neoplastic tissue The position of the tumour may be determined by the use of external counters with little disturbance to the patient The work described here is an advance in a difficult field, but it might perhaps have been more suitably published in shorter form, in plainer English, in a *specialised journal*

The Excitable Cortex in Conscious Man (London Liverpool University Press 1958 Pp 43 10*s* 6*d*)—This little book, which is a transcript of Dr Wilder Penfield's Sherrington lecture, gives a brief survey of some of his work, with various colleagues, on the response to electrical stimulation of the human cerebral cortex exposed after craniotomy under local anæsthesia The information obtained in this way is, as Dr Penfield is careful to emphasise, a by-product *of* surgical procedures undertaken with a definite therapeutic end in view *Two cases of epilepsy* in which elaborate psychical phenomena were elicited are described in some detail, but much of the book is devoted to an account in general terms of the properties of the cortical regions revealed by electrical stimulation and to schemata illustrating the author's interpretation of these properties If at times the argument seems a *little facile*, it must be allowed that in a necessarily abbreviated and primarily viva-*voce presentation* some elision is scarcely avoidable The book can be recommended not only as a convenient up-to-date summary of, but also a readily assimilable introduction to, the fascinating work done in the author's clinic

THE LANCET

LONDON 6 SEPTEMBER 1958

More New Steroids

The synthesis of new steroids, measurement of their effect in animals, and submission of selected examples to clinical trial are proceeding with increasing momentum Modifications of the cortisone or hydrocortisone molecule which have yielded substances of therapeutic interest have included the insertion of a double bond in ring A, a halogen atom at C19, and a hydroxyl or methyl group in the α configuration at C16 Singly or in combination these changes have produced substances of widely different character Fludrocortisone, the 9-α-fluoro- derivative of hydrocortisone,[1] is a much more potent "anti-inflammatory" agent than its parent steroid but is limited in its clinical applications by an even greater enhancement of sodium-retaining activity The unsaturated derivatives of cortisone and hydrocortisone, the δ or "predni" steroids—prednisone and prednisolone—are also more active anti-inflammatory agents than their precursors but have very little mineralocorticoid activity except in very large doses In addition to topical application 9-α-fluoro-hydrocortisone has a place in the treatment of some cases of Addison's disease and after adrenalectomy The δ steroids have largely replaced cortisone in the treatment of diseases such as rheumatoid arthritis and asthma, their weak mineralocorticoid activity is an asset, and in rheumatoid arthritis they promise to maintain control beyond the time when the effect of cortisone begins to wane

At the International Congress on Rheumatic Diseases last year the effects of a still newer steroid, triamcinolone, were discussed by Freyberg et al[2] This substance, prepared by Bernstein et al,[3] is hydrocortisone modified by a double bond in ring A, a fluorine atom at C9, and a hydroxyl group at C16 The last of these modifications converts a powerful mineralocorticoid into a substance with a sodium-diuretic action, its anti-inflammatory activity is slightly greater than that of prednisone or prednisolone Clinicians are unlikely to be impressed by the ability of a 4 mg tablet of triamcinolone to do the same good work as a 5 mg tablet of prednisolone unless the former has other advantages From several reports it is obvious that triamcinolone has some side-effects not shared with other steroids, among these Freyberg et al[2] mentioned severe headache, dizziness, anorexia, nausea, fatigue, and progressive loss of weight, but peptic ulceration did not occur In our columns this week Dr Dudley Hart and his colleagues report a comparison between the effects of prednisolone and triamcinolone in rheumatoid arthritis At a 4 5 dose ratio of triamcinolone to prednisolone the former was slightly more effective. Dyspepsia often persisted when triamcinolone was substituted for prednisolone, but no final conclusion was reached about the comparative risk of peptic ulceration Shelley et al[4] have reported that triamcinolone is effective in psoriasis—a disease which responds poorly if at all to other steroids Of 31 patients with systemic lupus erythematosus treated by Dubois[5] with triamcinolone, only 1 developed a new peptic ulcer, and a pre-existing ulcer healed during treatment with the steroid. Hart et al did not observe any of the unusual side-effects of triamcinolone except postprandial flushing Some of Dubois' patients, treated with much higher doses, developed profound weakness of muscles —particularly the extensors of the legs and the deep muscles of the back This disturbing effect was limited to women and slowly disappeared when prednisone or hydrocortisone was given instead of triamcinolone Furthermore many patients gradually lost weight—only partly from loss of fluid—and hirsutism and striæ were more prominent than in patients treated with other steroids The men in this series showed no "cushingoid" features, and for this reason Dubois believes that triamcinolone may be the steroid of choice in men. Of these patients with systemic lupus erythematosus most felt better during treatment with triamcinolone than with other steroids A hitherto unreported and unexpected effect of triamcinolone is described on another page by Dr Wells 3 patients treated with the steroid—1 for thrombocytopenic purpura and 2 for asthma—developed pains in their joints In 2 of these patients the appearance of the joints mimicked rheumatoid arthritis, in all 3 the arthropathy disappeared when prednisolone was substituted for triamcinolone It is conceivable that the patient with thrombocytopenic purpura had lupus erythematosus and that the joint symptoms were part of this disease, it is hard to explain their appearance during treatment with triamcinolone (but not with prednisolone) and equally difficult to explain the similar sequence in the patients with asthma The balance of evidence seems to suggest that arthropathy was a direct effect of the treatment. Clearly much more must be learnt about the advantages and disadvantages of triamcinolone It may at times be rather more effective than the δ steroids, it may (by virtue of its diuretic activity) be useful in patients with cardiac decompensation, and in those who gain weight rapidly, or whose blood-pressure rises, when treated with other steroids It shows considerable promise in psoriasis Further evidence is needed about the risk of peptic ulcer or osteoporosis—major bugbears of steroid therapy—although it has been claimed that it is less likely to provoke these effects than other steroids The muscular weakness described by Dubois may be troublesome only when high doses have to be used The unexpected effect in Wells' patients will clearly repay close study

Yet another new steroid has been brought into clinical use. This has the same structure as triamcinolone except that a methyl instead of a hydroxyl group occupies the 16α carbon position This substance, hexadecadrol ('Decadron'), synthesised in the laboratories of Merck, Sharp & Dohme, was used by Boland[6] in 21 cases of rheumatoid arthritis It proved to be 5–10 times as potent as prednisolone in controlling the disease, significant gastrointestinal symptoms did not develop, but the trial was preliminary and too brief for judgment of side-effects In animals the anti-inflammatory effect was 190 times that of hydrocortisone, but the glycogenic activity was enhanced by a factor of only 17. Sodium retention was not demonstrable in adrenalectomised rats The dissociation of anti-inflammatory and glycogenic activity, which are so closely related in other steroids, is striking, and reports on the long-term clinical use of this steroid will be awaited with interest

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[1] Fried, J *Ann N Y Acad Sci* 1955, 61 573

[2] Freyberg, R H, Berntsen, C A, Jr, Hellman, L, Gallagher, T F Paper read to 9th International Congress on Rheumatic Diseases, Toronto, 1957

[3] Bernstein S, Lenhard, R H, Allen, W S, Heller, M, Littell, R, Stolar, S M, Feldman, L I, Blank, H H *J Amer chem Soc* 1956, 78, 5693

[4] Shelley, W B, Harun, J S, Pillsbury, D M *J Amer med Ass* 1958, 167, 959

[5] Dubois, E L *ibid* p 1390

In assessing these products of the ingenuity of steroid chemists, potency is important only as a factor in the therapeutic ratio Dissociation of desirable from undesirable effects would be a great step forward

Thymectomy and Myasthenia Gravis

The association between abnormalities of the thymus and myasthenia gravis was recognised over half a century ago In most series of myasthenics rather more than a tenth have radiologically demonstrable enlargement of the thymus, and hyperplasia has been observed in over half the myasthenic thymuses examined histologically Nevertheless the precise relation between the thymus and myasthenia remains something of a mystery, for, although it would be easy to assume that the thymus produces a curare-like substance which interferes with neuromuscular transmission, it may be that an independent process, as yet unidentified, results simultaneously in the myasthenic state and enlargement or hyperplasia of the thymus The hyperplastic thymus may then in its turn accentuate and perpetuate the myasthenic muscular response The notion that myasthenia is accompanied by structural changes at the motor end-plate and is not necessarily due to some hypothetical thymic secretion is now receiving the attention it undoubtedly deserves, and we hope that the lead given by Woolf et al[7] proves profitable Wilson et al[8] showed that the myasthenic thymus has a high neuromuscular-blocking activity, and also that the greater the benefit of thymectomy in a given case the greater had been the blocking activity of that particular thymus On the other hand the thymus of children and of an adult who was certainly not myasthenic (this specimen was obtained at necropsy) also exhibited a high blocking activity Furthermore extracts of thymus from undoubted cases of myasthenia exhibited no high blocking activity In other words the link is not so obvious or so direct as some workers would have us believe The simple notion of thymic secretion fails to take into account the curiously selective affection of the ocular or bulbar muscles noted particularly by Grob[9] and by Ferguson et al,[10] and also seems difficult to reconcile with the fact that exercise of one part of the body may aggravate the myasthenic response in another[11]

Because of the conflicting physiological and pharmacological evidence we must turn to the evidence from clinical studies Is it in fact certain that surgical removal or radiotherapeutic destruction of the thymus is followed by significant improvement in myasthenia? Since Blalock[12] in 1939 reintroduced this operation, workers at various centres have considered the statistical evidence in the most careful and painstaking way In 1954 we concluded[13] that "until criteria for selection are improved, thymectomy will not commend itself for patients well maintained under medical management, those with localised ocular myasthenia, those in the older age-groups, or those with longstanding symptoms The choice of treatment remains most difficult in the young myasthenic with generalised symptoms and a short history Keynes's good results will influence some physicians in their choice, while the findings at the Johns Hopkins Hospital and the Mayo Clinic will make others hesitate" The allusion to Johns Hopkins related to the work of Grob,[9] who had concluded that there was no striking difference between the results of thymectomy and those of medical management, the Mayo Clinic workers were Eaton and Clagett,[14] who in 1950 had also found no significant statistical difference These two workers have since revised their opinion[15] Their initial conclusion that thymectomy had no significant beneficial effect seems to have sprung from their not at that time considering thymic tumours in a separate group Recent surveys have shown that in patients with such tumours the mortality is apparently not lowered by operation, which, however, may improve the myasthenic state for a time It seems possible that the best treatment in these cases may prove to be radiotherapy, for the postoperative death-rate is not inconsiderable Keynes[16] recommended surgery in these thymomatous cases only after radiotherapy had been applied, but alluded to three patients who remained well after radiotherapy without operation It is perhaps surprising that a tumour in the thymus should render removal of that organ less beneficial than in cases where there is no tumour, but this is in keeping with the generally paradoxical role of the thymus in myasthenia

Simpson[17] has now reviewed 404 cases of myasthenia comprising those seen at the National Hospital for Nervous Diseases together with those dealt with by Keynes in his extensive series of thymectomies Simpson was able to trace 374 of these 404 patients, and 245 of the 374 had survived Of these 245, 181 were re-examined, and the remainder completed a detailed questionary. The total series comprised 294 patients who had undergone thymectomy and 110 who had not been operated on. SIMPSON recognises the difficulties inherent in the statistical assessment and acknowledges that this series lacks any planned control, but feels that even so certain conclusions are justifiable. He expresses the opinion that this and the three American[9 14 15 18] series indicate that operation provides a worth-while improvement in prognosis for women with myasthenia, particularly by reducing case-mortality. In the London series women had a mortality of 15·4% from myasthenia or postoperative causes; and this certainly compares very favourably with the figure of 28·8% for deaths in the unoperated group. The figures for males suggest that operation reduced mortality hardly at all. As to the status of the survivors, it is clear that this differs widely at any given time both in the operated and in the unoperated. SIMPSON finds that in those not operated on mortality is higher in females than males, and that fewer women reach the higher categories of activity, whereas in those who have been operated on this trend is completely reversed. It seems that a shorter preoperative duration is likely to result in a higher physical status among survivors, but has little or no influence on the risk of death after operation.

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[6] Boland, E W *Calif Med* 1958, 88, 417
[7] Woolf A L Bagnall, H J, Bauwens, P, Bickerstaff, E. R *J Path Bact* 1956, 61 173
[8] Wilson, A, Obrist, O R, Wilson, H *Lancet*, 1953, ii, 368
[9] Grob, D *J Amer med Ass* 1953 153 529
[10] Ferguson, F R., Hutchinson, E C, Liversedge, L A *Lancet*, 1955, ii, 636
[11] Wilson, A, Stoner, H B *Quart J Med* 1944, 13, 1
[12] Blalock, A, Mason, M F, Morgan, H J, Riven, S S *Ann Surg* 1939, 110, 544
[13] *Lancet*, 1954, i, 352
[14] Eaton, L M, Clagett, O T *J Amer med Ass* 1950, 142, 963
[15] Eaton, L M, Clagett O T *Amer J Med* 1955, 19, 703
[16] Keynes, G *Lancet*, 1954, i 1197
[17] Simpson, J A *Brain*, 1958, 81, 112

With each new case of myasthenia the clinician must face the problem of whether to advise thymectomy or not in that particular instance. FERGUSON et al.,[10] reporting the results of the medical management of 75 patients, commented on the benign course of the ocular type of myasthenia—to which attention had been previously drawn by GROB,[9] who had followed 48 such cases for an average period of 8·5 years without encountering a single death. OSSERMANN et al.[19] suggest that juvenile cases of myasthenia gravis and those with highly localised manifestations do not need thymectomy, whereas the more generalised and acute types, progressive and unresponsive to medical treatment, may be submitted for thymectomy, but they do not give figures to indicate results. In the light of the present evidence it seems reasonable to conclude that young females with generalised myasthenia of short duration should be regarded as eminently suitable for operation, since among them operation results, in a significant saving in life and a lasting improvement in the myasthenic state. At the other end of the scale the patient with ocular myasthenia which has not spread to the general musculature within two or three years is likely to carry on quite well under medical management, and may in fact have a long spontaneous remission. When a tumour is present, radiotherapy will usually be preferred, though some workers recommend radiotherapy followed by operation. For the remainder it is impossible to generalise, the therapeutic plan will be conditioned by the personal views of the clinician, and by the patient's age, occupational and social circumstances, and personal wishes.

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18 Schwab, R. S., Leland, C. C. *J. Amer. med. Ass.* 1953, 153, 127

19 Osserman, K. E., Kornfeld, P., Cohen, E., Genkins, G., Mendelow, H., Goldberg, H., Windsley, H., Kaplan, L. I. *Arch. intern. Med.* 1958, 102, 72.

Annotations

UNEXPECTED DEATH IN INFANCY

IN infancy unexpected deaths have a special importance because of the distress they cause, often including tragic self-reproach by the parents. Though, by their very nature, they must commonly be unavoidable, even a small reduction in their number would be very well worth achieving. But better preventive measures must wait on better understanding of the reasons why babies die unexpectedly, and this is most likely to come from carefully planned studies by teams of experts. The inquiry into "sudden death" in infancy, organised by Prof. Leslie Banks, of Cambridge, at the request of the Ministry of Health, is therefore welcome, and his interim report, describing the work arranged by the very knowledgeable steering committee,[1] will command attention.

It describes, in fact, only a pilot investigation made in selected London areas, and in Cambridge and the surrounding district during the two years ended March, 1956. Moreover, since the main object was to gain experience for use in the subsequent full-scale investigation, alterations were made from time to time in the method of inquiry, in the routine for collecting material, and in the forms used for recording information. Hence what we are now given is to be regarded as no more than a report on progress, and its chief value lies in indicating the means by which such an inquiry may best be pursued and the lines of research which are likely to be most rewarding.

It is based on a study of 81 cases of sudden death between the ages of 2 weeks and 2 years, and the information obtained is considered in its pathological, microbiological, and social aspects. 64 of the infants died in London and 17 in the Cambridge area. In 38 of the 52 London infants examined histologically, evidence of tracheobronchitis was found, and in a proportion of these cases a special technique, not described in the paper, was used to demonstrate a characteristic tracheobronchial lesion. The tracheobronchitis was regarded as possibly of viral origin but viruses were actually isolated in only 2 of 50 infants examined for them. The remaining 14 London infants who were examined histologically had purulent respiratory infections, septicæmia, or gastroenteritis. In contrast, no definite "cause of death" was found in 13 of the 17 Cambridge cases, while infections (bronchiolitis, bronchopneumonia, septicæmia) were found in the other 4. Though the report does not compare the two series in detail, it seems possible that the London group of infants who had tracheobronchitis was similar to the Cambridge group in whom the cause of death was uncertain, and that the disparity in findings was due to differences in histological technique. On the other hand, the Cambridge workers may have been dealing with quite another problem, since the two groups differed (though perhaps not significantly) in sex-incidence, seasonal incidence, and the proportion of sudden deaths to all deaths at this time of life. It would be interesting to know more

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1 Banks, A. L. *Mon. Bull. Minist. Hlth Lab. Serv.* August, 1958, p. 152.

the criteria for diagnosing "tracheobronchitis, ...bly of viral origin" in the London infants, since interpretation of histological changes is always to some extent subjective [2, 3]

Bacteriological studies were made in 66 of the 81 cases, and in about half of these the lungs were sterile on culture or contained only the normal flora of the upper respiratory tract In most of the other cases, gastrointestinal organisms were cultured from the lungs, but the meaning of their presence is doubtful, since postmortem contamination could not be excluded Pathogenic organisms, including *Staphylococcus aureus* and *Hæmophilus influenzæ*, were found in 9 of the 66 cases The only conclusion drawn from the microbiological evidence was that infection with pathogenic bacteria is probably not an important factor in causing sudden death in infancy

Various workers have found a higher incidence of unexpected deaths during the winter months, and a preponderance of male infants [4] In the present inquiry both these observations were confirmed for the series as a whole and for the London series, though not for the smaller Cambridge series, in which the sex-incidence was roughly equal and cases occurred almost uniformly throughout the year The report suggests that poor general health, premature birth, illegitimacy, poor maternal care, or poor social circumstances, while not causes of sudden death, may increase the risk one or more of such handicaps was recorded in 44% of cases Accidental suffocation in a soft pillow or by overlaying caused few if any of these deaths, but the possibility that a considerable proportion followed the inhalation of food or vomit could not be excluded

A remarkable statement in the social section of the report is that cases of sudden death formed 25% of all deaths in the age-group and that in Cambridge the figure was as high as 44% This high proportion raises the question whether all these so-called sudden deaths would ordinarily be regarded as unexpected deaths Data from the Registrar General showed that, in 1955, 20 5% of deaths between the ages of 2 weeks and 2 years were "certified by a Coroner as being due to influenza, pneumonia, bronchitis, or other respiratory cause, or as due to obstruction, inhalation, ingestion, or accidental mechanical suffocation" Professor Banks' report says that these deaths are comparable to those considered in the inquiry, but this seems arguable For example, deaths due to ingestion would presumably include cases of accidental poisoning, whereas other accidents, such as road accidents, are considered as "clearly outside the scope of the investigation" The full account of this study could usefully define more precisely what is meant by the terms "sudden death" and "unexpected death" in infancy

The general conclusions of the committee so far are in line with most previous work in suggesting that, while the causes of sudden death in infancy are largely unknown, mechanical factors such as overlaying and accidental suffocation are comparatively rarely responsible, while respiratory infection, possibly by a virus, is an important factor in most cases Nothing emerged from the pilot investigation to explain why apparently mild infections should cause death in these infants, and this is perhap the crux of the problem [8] The results of the main inve tigation, based as it is on so much careful and methodical preparation, will be eagerly awaited

CARPAL BOSSING

CARPAL bossing was first described by Fiolle [5] in 1931, and since then the condition has rarely been noted outside France It consists of a painful prominence of the dorsum of the base of the third metacarpal and capi tate, visible on radiographs as a small exostosis and containing bone Most patients present with aching pain, a detectable bony lump, sometimes a bursa, and sometimes difficulties with snapping extensor tendons Recurrences after removal seem to be common [6] The single case described by Dorosin and Davis [7] and the two cases of Menegaux [8] suggest that this is a rare disorder In a small investigation of normal subjects Larson et al [9] have now shown that prominence of the third metatarsal base was rare in children but common in adults, and present in 50% of physiotherapists They suggest that the boss is due to new bone formation resulting from use It is clea that the deformity is common, but symptoms are rare, and treatment should depend on whether it is causing inconvenience

FOOD AND VOMIT IN THE LUNGS

THE aspiration of food and vomit has been investigated by Gardner [10] He introduced barium sulphate through a gastric tube into the stomachs of ten patients immediately after death The bodies were then transferred to the mortuary, and radiographs of the lungs were taken at the subsequent necropsies In seven out of the ten, barium had entered the lungs, reaching the alveoli in several Thus, unless the trachea is blocked as soon as the patient dies, necropsy evidence of antemortem aspiration cannot of itself be considered conclusive

Gardner then studied a series of ninety-four adult male and female patients who had either undergone a major operation or were debilitated for other reasons Each had non-flocculable barium sulphate added to all drinks—in the proportion of one part in six—for two to four days The lungs were repeatedly examined radiographically, and bronchoscopy was undertaken when clinically indicated Barium entered the lungs of ten patients (11%), but in most of them it was impossible to decide whether it was inhaled during vomiting or feeding

To distinguish the incidence of aspiration of vomit from that of aspiration of food, barium was given to a further fifty-one patients directly into the stomach through a tube, so that its appearance in the lungs could be due only to inhalation of gastric contents This occurred in only one patient Gardner concludes that aspiration of food is commoner than that of vomit (it took place probably in 9–10% of the patients studied as opposed to 1–2% for vomit)—and that it is often multiple Aspiration of either is often extremely difficult to diagnose clinically The overall results suggest that one in about every ten debilitated surgical patients inhales food or vomit

The complications directly attributable to aspiration are difficult to assess, but the fact that some patients in this

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2 Skogstrand, A *Acta path microbiol scand* 1957 41, 486
3 Stowens D *Amer J Dis Child* 1957 94, 674
4 Barrett A M *in* Recent Advances in Paediatrics (edited by D Gairdner) London, 1954
5 Fiolle, J *Bull Soc nat Chir* 1931 57 1687, *ibid* 1932, 58, 48
6 Carter R M *J Bone Jt Surg* 1941, 23, 935
7 Dorosin, N Davis J G *Radiology* 1956 66, 234
8 Menegaux, G *Rev Orthopéd* 1934, 21 231
9 Larson R L, Lazeano, M A, Janes J M *Proc Mayo Clin* 1958, 33 337
10 Gardner, A M N *Quart J Med* 1958, 27, 227

series undoubtedly died as a result of aspiration suggests that greater care is needed in posturing and feeding those who are very ill Gardner believes that aspiration of vomit or food is too often the coup-de-grâce—rather than an agonal phenomenon—in an ill patient who might otherwise recover He suggests that the standard hospital feeding cup, which is designed to facilitate feeding in recumbency, should be abolished as its style contributes to aspiration Not only does the shape of the spout enable fluid to be poured into the trachea, but the hooded top ensures that the patient is taken unawares The patient should either sit up and drink out of an ordinary cup or glass or lie on his side and drink through a straw If neither is practicable, feeding should be through a tube directly into the stomach The danger associated with vomiting can be offset only by the adoption of a prone or semiprone position

OCCLUSION OF ANTERIOR SPINAL ARTERY

THE syndrome of occlusion of the anterior spinal artery is of interest because of the striking clinical picture It was first recorded in life by Spiller,[1] who called the disorder syphilitic acute anterior poliomyelitis, having recognised the distinctive involvement of anterior horn cells at the level of the lesion This description of the necropsy findings is excellent For many years the condition continued to be regarded as a manifestation of syphilitic vascular disease, but it is now clear that many patients show no evidence of neurosyphilis, indeed the cerebrospinal fluid is often normal

Ten cases seen at the Mayo Clinic since 1949 have been described by Peterman et al [2] In three the lesion involved the lower cervical region, and in seven the thoracic region of the spinal cord The onset is usually abrupt and the clinical picture is fully developed within a few hours In the lower limbs, there is sudden loss of power often with pain across the shoulders, bladder and bowels are paralysed, and appreciation of pain and temperature is lost below the level of the lesion The posterior columns, subserving joint-position sense, touch, and vibration sensibility are spared In the cervical cases there are total lower-motor-neurone lesions of the muscles supplied by the segments involved—usually C7, C8, and T1 There may therefore be very severe permanent disability due to bilateral disruption of function of the upper limbs, particularly the hands In addition there may be segmental sensory loss, presumably due to ischæmia in the central grey matter of the cord Symptoms and signs are usually symmetrical The association of an anterior-horn-cell disorder at the level of the lesion with sparing of the posterior columns points to the diagnosis

The outlook for the lower limbs is fair In all but one of the ten Mayo Clinic cases the patient could walk after a few weeks, and control of bladder and bowels was regained Wasted muscles do not recover The anterior horn cells, which seem to be extremely vulnerable to anoxia, are permanently affected

Woollam and Millen [3] agree with Feeney and Watterson [4] that the nervous system has been developed to the limit of the vascular supply hence the havoc brought about by occlusion of the anterior spinal artery Radicular arteries from vessels adjoining the vertebral column vary from two to seventeen, and two of these (one cervical and one lumbar) contribute largely to the anterior spinal artery, which is formed by the fusion of two longitudinal chains The artery supplies the whole of the grey matter except part of the dorsal horn, and it partly supplies the anterior columns of white matter The lower cervical region and the lower thoracic region are most usually involved The reasons for this are not clear It is believed that blood flows through the anterior spinal artery, from both above and below, towards the thoracic region, and the sites of election may be watersheds Another possibility is indicated by clinical considerations Some patients with occlusion of this artery show no evidence of generalised vascular disease or of disease of the vertebral column Some seem to have engaged previously in physical work involving the shoulders and back, or to have suffered exposure The dependence of the anterior spinal artery on radicular contributions suggests that vasodilatation in the thoracic muscles may lead to ischæmia in the spinal cord The converse situation has been described in which the anterior spinal artery participated in the anastomosis consequent on coarctation of the aorta at the level of the ductus arteriosus [5]

In other conditions associated with vascular lesions of the cord, such as syphilis, vertebral fracture, aortic occlusion during operation, dissecting aneurysm of the aorta, and the aortic-arch syndrome, there are obvious pathological reasons for cord involvement In many cases of occlusion of the anterior spinal artery this is not so it is not even clear whether hypertension and atherosclerosis are important in this disorder The description of well-documented cases is still of great interest

"CLEAN" VERSUS CATHETER SPECIMENS OF URINE

IT is widely accepted that specimens of urine for bacteriological investigation from female patients should be obtained by catheterisation Besides causing inconvenience and occasionally embarrassment, this procedure carries a moderate risk of introducing fresh infection, and in fact it is often carelessly performed without regard for asepsis It has been suggested that technical perfection necessitates the presence of two nurses—one to separate the labia and clean the meatus, and the other to insert the catheter

Wishing to avoid the hazard of introducing infection Boshell and Sanford [6] advocate the examination of "clean" freshly voided specimens as an alternative, and claim that these specimens compare favourably in a bacteriological sense with those obtained by catheter The suggested procedure consists in thorough cleaning of the periurethral area in a Sitz chair filled with green soap solution, followed by gentle scrubbing with pads containing 'Zephiran' (1% solution of benzalkonium chloride) The patient then voids, holding the labia apart, and a mid-stream specimen is collected for culture The results in 67 cases corresponded closely with those from subsequent catheter specimens, and the technique is recommended as a screening method to reduce the need for instrumentation It may be questionable, however, how far such arrangements are appropriate in a busy outpatient clinic or hospital ward

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[1] Spiller, W G *J nerv ment Dis* 1909 36 601

[2] Peterman, A E, Yoss, R E, Corbin, K B *Proc Mayo Clin* 1958, 33 31

[3] Woollam, D H M, Millen, J W *Proc R Soc Med* 1958, 51, 540-550

[4] Feeney, J F, Watterson, R L *J Morph* 1946, 78, 231

[5] Blackwood, W *Proc R Soc Med* 1958, 51, 540-550

[6] Boshell, B R. Sanford, J P *Ann intern Med* 1958, 48, 1040

Special Articles

TREATMENT OF BREAST CANCER

THE QUESTION OF " SELECTION "

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The Lancet of May 31 carries a letter by Ian Mackenzie which relates to the comparison of the five-year survival-rate for a group of patients treated at the Mayo Clinic by radical mastectomy [1] with the five-year rate for a group of patients treated at Edinburgh [7] by simple mastectomy and radiotherapy A previous letter from George Crile, Jr ,[2] referred to by Dr Mackenzie, deals with the same matter, as do several other letters

Comment on the comparison can be misleading without an explanation of the context of the analyses

CRITICISM OF RADICAL MASTECTOMY

The report from the Mayo Clinic, in its primary section, set forth the results, in the form of survival-rates, for a group of 9649 patients with mammary cancer who had been treated surgically over a period of almost half a century, from 1910 to 1954 In all but a negligibly few cases the treatment was by the classical radical mastectomy of Halsted (supplemented in designated cases by irradiation)

In the last couple of decades radical mastectomy has come under severe criticism In particular, McWhirter's [4,7] analysis of its putative deficiencies has led him to conclude that it should be abandoned Since 1941, under his direction, patients at Edinburgh have been treated instead by simple mastectomy and radiotherapy, with results [4–7] which he regards as better His reports have had a significant influence in the United States, and, though the superiority of simple mastectomy and irradiation has not been explicitly accepted, his arguments have undermined confidence in radical mastectomy Surgeons whose training and experience do not permit them to perform the radical operation have found in them support for performing only simple mastectomy, and some therapeutic nihilists have found support for arguing even that all treatment of cancer of the breast is futile These views have permeated to young physicians beginning their careers and (even more important) to the general public, and the effect has been confusing and demoralising Veritably an ominous situation was developing Since our own results with radical mastectomy, though not ideal, did not reflect the dire predictions of McWhirter's theoretical analysis, we felt obliged to make a careful examination of his reports In the second section of our article we presented a critical analysis based on this examination

We may remark, with entire objectivity, that this examination was undertaken with no animus toward Dr McWhirter or bias against his bold experiment On the contrary, we all had been impressed with the admirable thoroughness of its implementation, and the simple clarity and completeness of his statistical reports More than once, one or other of us actively participated in making an opportunity for Dr McWhirter to present h case However, it is necessary to note that systemat reading of his articles reveals a disquieting characterist in them whenever he had occasion to refer to favourab results obtained with radical mastectomy, he explici imputed " selection " to that series Thus, writing of report of Harrington, he said " Some degree of selectio may be presumed, for in 40% of the cases microscop examination of the axillary glands did not show involv ment " [4] Now it is not obvious why an incidence of 60 with axillary metastasis should imply " selection " I fact, the choice of this statistic as evidence of " selection ' proved an unhappy one, for another paper [7] stated th when radical mastectomy was performed in Edinburg before 1941, the proportion of cases found with axilla metastasis was just 60% The imputation of selection sometimes couched in terms suggesting prejudice, when McWhirter [4] said

> " Unfortunately the extent of failure of the radical operatio is too often concealed by presenting only the results obtaine in highly selected cases By selecting cases for the radica operation very carefully and by publishing the results only i the cases so selected the survival rates may be made to appea so good "

Or again [6]

> " There is no more certain method of securing good result than by careful selection of patients for treatment it is no uncommon to limit the use of a method to early cases and t apply some alternative method in the more advanced cases *Thus as the limitations of radical mastectomy* become mor clearly recognised, it has become customary to restrict th operation to early cases and to refer all the more advance cases for treatment by roentgenotherapy "

The last statement is fairly in reverse of the experience o the Mayo Clinic, where radical mastectomy has been th undeviating basic policy of treatment, and the proportio of patients found inoperable has been in steady decline It appears also to be in contradiction of general experience, as reflected in a recent report from Connecticut,[8] where it was found that use of the radical operation is increasing, radiotherapy decreasing, and the survival-rate improving

In reaching his conclusion that simple mastectomy and irradiation is superior McWhirter did not compare his results with those of contemporary treatment by radical mastectomy He compared them with those of radical mastectomy as practised in Edinburgh before this new treatment policy was instituted The chief part of our critique of McWhirter's report consisted in an analysis of the fallaciousness of this comparison, with its reasoning *post hoc ergo propter hoc* Our own results from the Mayo Clinic over the long period studied, during which there was no material change of treatment, showed progressive improvement So did other results quoted from the literature, and (as could be fairly clearly demonstrated from the admirably detailed statistics given in McWhirter's early reports) the results in Edinburgh also show improvement which was independent of change of treatment As is apparent from independent evidence, this improvement is mainly due to patients coming for treatment earlier in the disease—a result, we believe, of the cancer-education campaign by " lay " organisations Our point here, then, is this McWhirter's claim that simple mastectomy with irradiation is better than radical mastectomy was based on a fallacious demonstration

EDINBURGH AND ROCHESTER

It was natural, however, that we should try to compare our results with those reported by McWhirter We were very conscious that the results in the two series, taken on their face, were not validly comparable. In particular, since we had noted an improvement in our results with time, and since a similar improvement could reasonably be assumed in McWhirter's experience, it would not be "fair" to include results of our experience later than those represented in his report. We segregated our cases in which treatment was given in the same years as those reported by McWhirter—namely, 1941–47. Now what cases of these years should be included? McWhirter often stresses that all cases should be included. But we thought this should mean all cases "coming under treatment within the respective treatment policy". In making comparative studies this is what is generally done, and it seems to be what McWhirter does. In his table v, all the cases (1882) are included, segregated into several groups, but this is a bookkeeping table. In table vi, which is concerned with the influence of age on survival, cases categorised as having distant metastases are omitted. Here McWhirter is proceeding as one normally does—for purposes of comparative analysis one uses only the treated patients. We included only his 1609 cases without distant metastases (1882 less 273 having distant metastases) to represent his series coming under treatment, but of course we included *all* of them. The results in these cases were compared with the results in *all* our cases in which radical mastectomy was performed during the same period, which numbered 1918. It is this comparison that is being brought into question.

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We believe this comparison, using only the patients coming under treatment, is the most meaningful one, but in present circumstances we think it to the point to make the comparison including literally all patients—i.e., including McWhirter's 273 patients (15%) who did not come under treatment, and the 362 patients (16%) in the Rochester series found inoperable, that is, patients who did not have a radical mastectomy because of the advanced character of the cancer. There is a mechanical difficulty here, because in Rochester we do not regularly follow up the untreated patients, and so we do not know the number of five-year survivals among them. We made the calculation on the assumption that the survival-rate among these inoperable cases was 4·4%, which is the survival-rate recorded by McWhirter for the comparable 273 cases of his series; we also present the figures assuming that this survival-rate was zero. The results are shown in the accompanying table. Whichever way the comparison is made—for the entire series or for the group representing the treated patients—the conclusion is essentially the same. The five-year survival-rate for the patients dealt with under the policy of radical mastectomy exceeds that for the patients dealt with under the policy of simple mastectomy and irradiation: it exceeds it by what amounts to about 20% of the survivals achieved in Edinburgh. Recalling McWhirter's reiterated emphasis on selection, we may note that in a review[9] of all (i.e., unselected) cases of cancer of the breast in Connecticut in 1941–47, the five-year survival-rate averaged 51·3%; for the Edinburgh series in the same years it was 41·8%.

COMPARISON OF FIVE-YEAR SURVIVALS, TREATED AND TOTAL SERIES

Patients	Edinburgh		Mayo Clinic		
	No	Lived 5 years or more	No	Lived 5 years or more	
		No		No	No
Subjected to treatment policy*	1609	774 (*48·1%*)	1900‡	1127 (*59·3%*)	1127 (*59·3%*)
Not subjected to treatment policy†	273	12 (*4·4%*)	362	16§ (*4·4%*)	0¶ (*0*)
Total	1882	786 (*41·8%*)	2262‡	1143 (*50·5%*)	1127 (*49·8%*)

* In this group, as respects both series, are included the patients used in the original comparison.

† For the Mayo Clinic series these are the patients not receiving radical mastectomy; for McWhirter's series, they are the patients "with distant metastases present".

‡ 19 patients not traced for five years are omitted.

§ Assume 4·4% survived.

‖ Adjustment for hospital death-rate of 0·6% will lower this to 58·9%.

¶ Assume none survived.

Does this establish definitely that radical mastectomy has a higher survival-rate than simple mastectomy with irradiation? In particular can we be certain that the Edinburgh series as a whole, or the group of patients coming under treatment, is not generally of a more advanced cancer? We did not say so. We described the problem of the comparability of cases as "the devil's own question". We carefully considered the data that bore on it, and concluded that the two series could reasonably be regarded as fairly comparable. But in the end we wrote:[1]

> "But when all is said, on this matter of the selectivity of the cases, that can be said, it must be admitted that we really do not know with certainty how important a factor it is in accounting for the difference in survival rates reported in the literature. We agree with Atkins that, in order to evaluate the relative efficacy of radical mastectomy and the projected policy favoring simple mastectomy with radiotherapy, McWhirter missed an opportunity to initiate a controlled clinical trial. . . ."

What is the burden of Dr. Crile's criticism, which is a replica of the criticism made by Dr. McWhirter himself, in some personal communications received before publication of Dr. Crile's letter? In essence it is that the Mayo Clinic cases are favourably selected; specifically it is that we should not have used the total 1609 cases of McWhirter's series as we did. It is suggested that we should, instead, have used only the 1063 cases which he enumerated under the rubric "operable"—which here means operable by radical mastectomy, an operation not performed in Edinburgh. These 1063, however, constitute only 56% of the total 1882 of McWhirter's series,† and it is suggested that they are the ones that should be compared with our 1918 cases treated by radical mastectomy, which constitute 84% of the total 2280 of the Mayo Clinic series (table). This is hardly in keeping with McWhirter's repeated admonitions that, in reporting results, all cases should be included. The 546 cases of his series which he would have us omit on the ground that at the Mayo Clinic they would be regarded as too advanced for radical mastectomy, are enumerated under the rubric "locally advanced"—defined as having "complete fixation of the primary tumour to the pectoral fascia or to the ribs, fixed nodes in the axilla, enlarged supraclavicular nodes or widespread involvement of the cutaneous lymphatics over the breast, but no evidence of more distant metastases "[7]

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† To accept this suggestion would imply that, among women with mammary cancer who come from South East Scotland to Edinburgh for treatment, the disease is so far advanced that it is "inoperable for radical mastectomy" in 44% of cases. This would be a severe indictment of cancer education in that country in respect of early recognition and treatment, if it does not, instead, imply a conception of inoperability which reflects an extreme prejudice against radical mastectomy. McWhirter's conception of the effectiveness of this operation is clearly given when he says:[4] "When radical surgery is the only method of treatment available and when all cases coming (whether admitted or not) to a large general hospital are considered I do not believe the five-year survival rate will be found to be higher than 20% to 25%." The validity of his estimate may be gauged by contrasting it with the results reported[9] for the general population of Connecticut.

Such definitions are fairly easy to formulate but very difficult to apply in a uniform standard way, even within a single clinic—much less in different institutions in different countries ‡ The indications for radical mastectomy at the Mayo Clinic are very generous, and we believe that we perform this operation regularly with patients who would be placed in the above category In at least one publication[4] McWhirter considered cases of Manchester stage *III* as operable, and such cases comprise about half of those he includes in the category "locally advanced ", though they do not correspond to the quoted definition of this category This will illustrate the element of arbitrariness inherent in deciding which cases are "*inoperable for radical mastectomy*" A proposal[9] to institute an international classification of stages is, in theory, sound But if the classification is to be used for standardising the comparison of survival results, it may in practice introduce more confusion than clarification If method A has a better survival record than method B for all cases, but method B has equal or almost equal results for the cases classified as "operable ", then the general problem of comparability is complicated by the additional problem of applying the classification uniformly If the criteria of "operable " have been defined *in the first instance* by an advocate of B, then the task becomes perplexing indeed It is only human that an advocate of B should think that a particular patient who is not likely to do well by that method would certainly not do well by A Better results with A, except in a controlled experiment, cannot be considered proof that A is really the preferable method to use invariably, many other elements have to be taken into account But the argument that method B's inferior results automatically prove that patients subjected to method A are selected is not acceptable § In our analysis of the Mayo Clinic series, the designation of a case as "inoperable ", *for purposes of computing an inoperability rate*, is not an expression of opinion about its suitability for operation it means that radical mastectomy was not in fact performed Likewise, we did not refer to cases which were "operable " but only to patients who were operated upon by radical mastectomy

The suggestion that our cases should be compared only with the 56% of McWhirter's series enumerated under the rubric "operable " is reminiscent of a procedure occasionally used by physicians, by which a method of therapy is advocated as effective but "only in properly selected cases ' Results are then presented, but only for the properly "selected cases " We do not think this is a good procedure, we think that all patients coming under treatment should be included

The Mayo Clinic series, taken as a whole, may in a sense be considered "selected " The practice of this clinic is, to a considerable degree, a referred one, and patients are referred for treatment from all parts of the country But when local doctors make selection between patients with early or advanced disease, it is those with the more advanced disease and less hopeful outlook who are selected for referral, and our clinic is sometimes dubbed as a "court of last resort " The patients who come for treatment represent a wide spectrum of degrees of advancement of the cancer Early cases do appear, and happily the proportion of patients coming for treatment early in the disease is increasing—a result, we believe, of the cancer educational campaign But very advanced cases are also received, including moribund patients, in no small number, admitted to the hospital only to die there It is necessary to make this rather graceless statement, because in some quarters our results in cancer of the breast are disregarded on the ground that we deal only with "selected " early cases If, because of this misconception, erroneous judgment is made as to the relative efficacy of different methods of treatment, it is the patients who will be the victims

REFERENCES

1 Berkson, J , Harrington, S W , Clagett, O T , Kirklin, J W , Dockerty, M B , McDonald, J R (1957) *Proc Mayo Clin* 32, 645
2 Crile, G , Jr (1958) *Lancet*, i, 739
3 Mackenzie, I (1958) *ibid* p 1171
4 McWhirter, R (1948) *Proc R Soc Med* 41, 122
5 — (1948) *Brit J Radiol* 21, 599
6 — (1949) *Arch Surg* 59, 830
7 — (1955) *Brit J Radiol* 28, 128
8 Newell, R R , Chamberlain, W E , Rigler, I (1951) *Amer Rev Tuberc* 69, 566
9 Ryan, A J , Griswold M H , Allen, E P , Katzenstein, R , Greenberg, R , Keogh, J , Wilder, C (1958) *J Amer med Ass* 167, 298

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‡ To gauge the difficulty of setting up a *workable* classification of the advancement of disease, even in the relatively objective situation of the reading of X-ray films, one may profitably study an article[8] by Newell, Chamberlain, and Rigler, entitled Descriptive Classification of Pulmonary Shadows

§ McWhirter has presented a semantic case against radical mastectomy which is well-nigh invulnerable He begins with the premise that radical mastectomy *must fail in a large majority* of cases, variously estimated as from 64% to 80%[4 5 7] If now one presents favourable results *with radical mastectomy*, it only makes the case worse for radical mastectomy Because—so the argument goes—since we know that radical mastectomy is an ineffective operation, then favourable results reported with radical mastectomy can be the result only of the surgeon's selecting the early cases and passing on the advanced cases to the röntgenologist for palliative treatment Now the surgeon would not do this if the operation were *effective* Hence, in this argument, good results prove the ineffectiveness of the operation

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Occasional Survey

INFECTION ACROSS THE INTACT CONJUNCTIVA

H Stanley Banks
M A, M D Glasg, F R C P, D P H

The mounting evidence that the conjunctiva may be the route of natural infection in certain virus and bacterial diseases seems to have attracted little attention

The first practical application of this concept was in North Africa In 1930 Anderson and Gerard,[1] in a preliminary experiment, instilled convalescent serum into the eyes of 30 contacts of measles three times daily for eight days, and none developed measles during eighteen days of observation, no controls were mentioned and no further report has been traced A few years later Sicart[2] attempted to control an outbreak of measles in a residential school by the method of Anderson and Gerard, but out of 24 contacts treated 11 developed measles As the latter were in the sixth day of the incubation period when the instillations were started, this failure is not surprising

In 1954 Karola Papp[3] put the matter on a more scientific basis She transmitted measles across the intact conjunctiva in 5 out of 6 susceptible children by means of saliva taken from cases of measles in the first three days of the eruption On the other hand, no result was obtained in 9 susceptible children whose buccal mucosa and tonsils were painted with infective measles saliva, and only 2 out of 13 such children developed measles when the infective

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1 Anderson, C , Gerard F *Arch Inst Pasteur, Tunis*, 1930, 19, 435
2 Sicart, M *ibid* 1936-37, 26, 266
3 Papp, K *Rev Immunol* 1954, 18 380

saliva was instilled into the nose. In all these cases the saliva was well diluted with normal saline With the same technique in mumps 2 positive results in 10 trials were reported, but failure resulted in 6 cases out of 6 when the infective mumps saliva was painted on the buccal mucosa and tonsils Rubella was similarly transmitted across the conjunctiva in 2 cases out of 6, but no success was obtained with chickenpox transmission in 21 instances, both saliva and fluid from vesicles being used None of these instillations produced any local reaction

Papp pointed out that the fine superficial capillary network in the conjunctiva, draining into the deep network by relatively large venous channels, probably favoured absorption of infectious material, in contrast, the capillary network in the nasal mucosa was much coarser, one of its main functions being to warm the inspired air She also suggested that the success of the experiments of Anderson[4] in transmitting rubella by infectious material sprayed into the mouth, might be due to the infection reaching the eyes as well as the mouth

Papp[5] next attempted to prove that the eye was the *sole* route of natural infection in measles In each of three trials, 3 susceptible children, whose eyes were completely protected by goggles closely sealed to the face, were placed in contact with highly infectious cases of measles, and *none of these contacts developed measles* Although this experiment was uncontrolled, the very high infectivity of measles in the early acute stage makes this result indeed remarkable In a second experiment four groups, totalling 18 susceptible children, after exposure to undoubted measles infection, had one drop of convalescent serum instilled into each eye—in 15 cases one to six hours after exposure to the infection, *none of these 15 children developed measles* In the remaining 3 cases, where the instillations were made seventeen to twenty-four hours after exposure, 2 developed modified, and 1 unmodified, measles

This year Rusu[6] has reported strikingly successful results with Papp's method in the prophylaxis of measles, mumps, and chickenpox, when these infections were introduced into a children's sanatorium containing many susceptibles Of 69 children believed to be non-immune, all were protected from measles, as well as 58 from chickenpox in one experiment and 29 in another, and 57 from mumps in one experiment and 61 in another Moreover 12, believed to be susceptible to both mumps and chickenpox, when exposed to both diseases, contracted neither The only failure reported was among 22 children exposed to 2 different cases of chickenpox on successive days, in this group 2 developed chickenpox on the seventeenth day Unfortunately none of these massive experiments were controlled

Relevant controlled experiments in guineapigs have recently been reported by Moore[7] He has produced striking quantitative evidence that the conjunctival route is far more effective than the oral route in producing systemic salmonella infection This finding was confirmed by exposing animals wearing effectively sealed goggles, and also control ungoggled animals, to environments heavily contaminated with *Salmonella enteritidis*, the former were found to be highly resistant to infection, while the ungoggled controls showed high infection-rates It was also found that conjunctival swabbing was more effective than rectal swabs for detecting the spread of this infection, and eye-swabbing combined with segregation of eye-positive guineapigs and their cage-mates was apparently successful in controlling two *Salm enteritidis* epizootics Moore's final remark seems to me to deserve wide publicity "It may well be that the conjunctival route is worth considering in the epidemiology of bacterial and virus infections of man"

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[4] Anderson, S G *J Immunol* 1949, 62, 29

[5] Papp, K *Rev Immunol* 1956, 20 27

[6] Rusu, J *ibid* 1957, 21 393

[7] Moore, B *J Hyg, Camb* 1957, 55, 414

Congresses

GENETICS

The Tenth International Congress of Genetics was held in Montreal on Aug 20–27

Population Genetics

T Edward Reed (Ann Arbor, Michigan) discussed the stability of Huntington's chorea It had been suggested that the condition may be increasing as afflicted persons were more than usually fertile This inference was erroneous, and support for it was due to the fallacy of regarding the unaffected siblings as a suitable control Not only would they not know that they would be unaffected at their period of highest fertility, but they would also tend to be younger A comparison of the fertility of persons with Huntington's chorea and the remainder of the population standardised for age showed that the carriers of the gene were not producing children at as high a rate as the remainder of the population of Michigan

Jessica H Lewis and C C Li (Pittsburgh, Pennsylvania) presented data on the families of persons with hæmophilia A and B Type A, which represented 84% of the 116 cases, was the classical hæmophilia, type B was sometimes known as Christmas disease There was strongly suggestive evidence of a disturbed sex ratio, and also a disturbed segregation ratio of the defective gene, in each case the disturbance was such as to increase the dissemination of the harmful gene, and a gene which could load its chance of segregation could be stable although disturbing the viability of its host

Cytology

T T Puck (Denver, Colorado) demonstrated the feasibility of culturing human cells derived from minute skin-biopsy specimens These cells remain in good health for months, and a 20-hour division cycle provides unlimited numbers, the chromosomes retain their individuality, and colchicine inhibition makes their detailed study practicable The elaboration of suitable media should allow chromosomal investigation to be made from material acquired and cultured with the simplicity of a throat swab

Using these methods of culture, J H Tjio (Zaragoza, Spain) and also E H Y Chu and N H Giles (Yale) have made extensive studies of the chromosomal complement in man No cells showing 48 chromosomes were observed In subsequent discussion of these papers J L Hamerton (London, England) suggested that, in view of the consistent preponderance of expert opinion, and the absence of public evidence to the contrary, 46 should be regarded as the basic chromosome number in man Tjio and Chu claim that the individual chromosomes in man can be distinguished, and they have each advanced a separate nomenclature.

B M Slizynski (Edinburgh) presented data on the frequency of chiasmata in the oocytes and spermatocytes of mice, chiasmata are about 15% more frequent in the female, implying a slightly looser linkage

A Bajer and J Bajer-Molé (Cracow, Poland) showed a film of mitosis in living plant cells, including detailed studies of normal mitosis followed by the aberrations induced by irradiation and colchicine The mechanism of mitosis, which is similar in all the higher plants and animals, has not previously been demonstrated at such a standard of technical excellence

Colour-blindness

H Kalmus (London, England) showed a film revealing the world as it looks to the colour-blind The film was made under the direction of a woman colour-blind in one eye

New Individualities of the Blood

Sylvia Lawler (London) presented data confirming the specificity of Gm serum-protein groups in man A Gm-positive serum is defined as that which will inhibit the agglutination of specially sensitised red cells by the serum of patients with rheumatoid arthritis Data from numerous families were consistent with inheritance as a single factor, active in the heterozygote, and not closely linked with other blood-group loci

O Smithies (Toronto) presented an extensive series of two-dimensional starch-gel electrophoretic blocks demonstrating previously unrecognised variation in the constituents of the β-globulin fraction of the plasma While almost all Canadians tested showed only one type (C), a very few having type B also, a high prevalence of type D was found in a sample of Australian aborigines, and some specimens showing this type were obtained from New York Negroes Three alleles are postulated, and these appear to segregate independently of those determining the major blood-groups There is highly suggestive evidence of identity between these β-globulins and transferrin

Blood-groups and Disease

C A Clarke and P M Sheppard (Liverpool) presented their extensive data on the blood-group and secretor status of siblings of patients with duodenal ulcer The increased liability of group-O persons and of non-secretors to duodenal ulcer could not be demonstrated within these family groups The apparent partial protection enjoyed by secretors is unlikely to be a non-specific effect of swallowing polysaccharides, as the quantity in the saliva of non-secretors, estimated by the fucose method, is almost as high as in secretors Specific absorption of ABO antibodies could be demonstrated on the exfoliated duodenal cells of secretors

Clarke and Sheppard also presented extensive data consistent with the hypothesis that the common form of erythroblastosis fœtalis is consequent on a previous pregnancy in which the baby was both rhesus-positive and compatible as a donor to the mother relative to the ABO system

J Buettner-Janusch, S J Behrmann, and F P Thieme (Ann Arbor, Michigan) had studied the ABO blood-group and the secretor status of the saliva and semen, using McNeill's techniques, of apparently sterile men Defining an aberrant secretor as a man not secreting in his semen at least one of the ABO(H) substances present in his saliva, a high proportion of aberrant secretors were found in sterile men, many of whom showed defective spermatogenesis None was found in a sample of fertile men Evidence was also presented suggesting that husband-wife ABO incompatibility may be a cause of infertility or reduced fertility, in the latter case the children included many more of group O than would be expected if the survival of the zygote were unrelated to its blood-group

J A Fraser Roberts (London, England) reviewed work on the associations of blood-group and disease, and presented new data The original claims of an association of the ABO blood-groups with duodenal ulcers, gastric ulcers, and carcinoma of the stomach have been consistently confirmed in so many centres that their reality must be accepted A distinct association on extensive data from one centre had been reported for tumours of the salivary glands, and this could to some extent be regarded as supporting the reality of associations of the ABO groups with carcinomas of the intervening œsophagus, and of the structurally similar pancreas There was also suggestive evidence of an association with diabetes mellitus Fraser Roberts drew particular attention to the inconsistencies between reports on other conditions from various centres Some of these inconsistencies could hardly be fortuitous, and their interpretation, while probably more difficult, might be even more important than that of the clear-cut and consistent associations found in various disorders of the upper alimentary tract

The Uterine Environment

A McLaren and D Michie (London, England) reported that on transplanting fertilised mouse ova into a foster-mother there was clear evidence that the number of lumbar vertebræ in the embryo tended to resemble that of the foster-mother more closely than that of either parent The stage at which segmentation is determined excludes any simple mechanical or nutritional explanation

K -H Degenhardt (Munster, Germany) demonstrated the consequences of exposing rabbits to an oxygen tension equivalent to that at 28,000 feet for four hours on the 9th day of pregnancy A primary disturbance of the cell metabolism of the notochord predisposes to a generalised disturbance of the central nervous system and its surroundings somewhat similar to those found in anencephaly in man

Dorothy Warburton (Montreal) presented data on the factors influencing the spontaneous-abortion rate in man. The incidence in relation to a history of previous abortion varied smoothly between 14% in women who had not previously aborted and 26% in women who had had three previous spontaneous abortions In relation to maternal age there was a smooth increase from an incidence of 12% in women under 25 years to 23% in women aged 40–44 years A history of prematurity of previous infants appeared to be associated with an increased risk of abortion Congenital deformities did not appear to be associated with a difference in incidence of abortion of other pregnancies, with the exception of cleft palate which was associated with a distinctly lower abortion-rate No increased risk could be demonstrated in consanguineous marriages

Familial Concentrations of Joint Disease

M Whittingill, E H Hendricks, G S Taylor, and L S Thorpe (Chapel Hill, North Carolina) demonstrated a vast single pedigree involving 3000 persons with special reference to the distribution of rheumatoid arthritis, Still's disease, and spondylitis Within the family as a whole the incidence of these diseases was comparable to that in the general population, but there was a definite several-fold increase in incidence in close relatives of affected persons While relatives of cases of rheumatoid arthritis were particularly prone to rheumatoid arthritis, and relatives of cases of spondylitis were particularly prone to spondylitis, there was no tendency for relatives with one disease to be predisposed to the other All fourteen cases of Still's disease were found in parts of the family unaffected by rheumatoid arthritis, and most were in close relatives of patients with spondylitis Consanguinity also appeared to predispose to this disease A remarkable but possibly fortuitous finding was that 14 cases of harelip were found, all in parts of the family unaffected by rheumatoid arthritis

Detection of Carriers of Recessive Genes

D Y-Y Hsai, S G Driscoll, and E M S Gawronska (Chicago) discussed the advantages of being able to discriminate the heterozygous carriers of recessive genes In phenylketonuria the estimation of the tyrosine-phenylalanine ratio allowed almost complete discrimination between these carriers and the normal heterozygote In cystic fibrosis of the pancreas the sodium content of the sweat, although intermediate between that of the two homozygotes, was too variable to allow reliable discrimination In the much rarer conditions of galactosæmia and von Gierke's disease evidence of impaired enzymic activity could be demonstrated in blood from most known heterozygotes, but this was not, at present, reliable as a method of discriminating carriers outside affected families

H Harris and E B Robson (London, England) presented extensive data on the families of patients with hypophosphatasia Urinary chromotography showed that the majority of presumptive heterozygotes could be detected by their excretion of ethanolamine phosphate, while this metabolite could not be detected in a large series of controls The proportion of heterozygotes excreting this varied greatly between different families

Influence of Radiation in Man

H J Muller and T Dobzhansky, approaching the problems of the atomic age from their diverse theoretical standpoints, urgently drew attention to the future implications of diagnostic, industrial, and military irresponsibility—a theme later incorporated in a resolution by the congress as a whole Muller's interpretation of the hazards to be anticipated is that the general viability of the entire race will suffer, the main effect being on the vigour and longevity of adults Dobzhansky, also arguing by analogies predominantly derived from the fruit-fly, sees no likelihood of any generalised impairment of health and bases his anxieties on the moral problem that the dissemination of atomic waste is largely in the hands of men who are prepared to expose the unborn to the unknown There appears to be no informed doubt that the unborn have been, and will be, irretrievably exposed to the risks of recessively determined diseases on a scale previously associated with the execution rather than the preparation of war While the numbers are large the proportions are so small that, even at the sites of the atomic bombs used in war, only in rice has unexceptionable evidence of unequivocal genetic change been demonstrated

Medicine and the Law

Press Publicity before Trial

WHEN a criminal charge comes before the magistrates, it may be dealt with summarily that is, the magistrates will decide whether the accused is guilty or not, and, if they find him guilty, decide upon sentence In serious cases, however, the magistrates perform a different function They decide whether there is a prima-facie case against the accused, and, if so, they commit him for trial before a jury at assizes or sessions The magistrates have power to sit privately when doing this, but they nearly always sit in public, and the press can report the case fully

Committal proceedings before the magistrates have not always been held in public Before the days of organised police forces, the magistrates had the responsibility of arresting offenders, and, in deciding whether or not to commit for trial, they were also in effect performing a function now normally undertaken by the police—namely, deciding whether the accused should be charged at all But, for the past hundred years or so, committal proceedings have nearly always been heard in public, and this has been felt to be in the best traditions of British justice

There is a risk, however, that disclosures in the magistrates' court may prejudice the trial before the jury Evidence may be brought before the magistrates, and widely reported, which is not in fact used at the trial This happened in last year's trial of Dr John Bodkin Adams Before the magistrates, the prosecution led evidence of the circumstances in which two other patients had died, this evidence was not given at the trial Moreover, there is some unfairness to the accused in that he may, quite properly, decide to reserve his defence—with the result that the press can report only the prosecution's case before the magistrates Even if this does not attract such nation-wide publicity as that given to the Adams case and some others, a jury may be prejudiced by what they have read in a local paper

After the Adams trial, the Lord Chancellor appointed a committee, with Lord Tucker as chairman, to consider possible remedies[1] This committee is firmly against extending the number of hearings in private It regards this as undesirable and unnecessary because the same end can be reached by restrictions on the right to report The committee recommends that, unless the accused has been discharged, or until the trial is over, any report of committal proceedings should be limited to particulars of the name of the accused, the charge, the decision of the court, and similar facts This recommendation cannot be put into practice without legislation

In England Now

A Running Commentary by Peripatetic Correspondents

IN a little over two years I shall be 65, and Parliament has decreed that I shall be unfit by reason of age to treat patients in the Health Service and to teach medical students I propose then to go to the bar, and "with a little bit of luck" I hope to become Lord Chief Justice in my early 70s I may—but I make no promises—retire from that post when I am 81, but if I do I shall continue to sit as a judge in the Privy Council and the House of Lords, where, of course, I shall also help to make the laws—such as that one about consultants retiring at 65

* * *

The path through Blossom Wood is vanishing When we came, three years ago, it was not uncommon to see small parties of people wandering along it as it cut diagonally across the hanger beyond the stream at the foot of our garden Sometimes they came from a picnicking car left where the path begins as a track higher up the lane sometimes they were locals on a Sunday afternoon stroll or children lured by the bluebells in spring or the stately summer foxgloves Last year there were fewer and now only a man with a gun is rarely seen

Though it is a bridle-path marked on the official parish map, the farmer has wired up the far end to prevent his cattle straying into the wood, where one broke a leg recently—it is easier and cheaper than putting a stile or a gate But the real reason for its rapid decay is Ted's purchase of a motor-bike on the never-never Twice a day he used to walk along it to and from his work, and that was enough to keep it clear without conscious effort on anyone's part Now the brambles spread across like thin green snakes, in places the bracken was shoulder-high this lush year, and in the little central groove where there used to be hoof-marks the young alders and birches are two feet tall and more I have just spent a hard morning clearing my favourite part, from where the path from the ford in our garden joins it to the sunlit clearing where a great spotted woodpecker often clings in his uniform of black, white, and red like the Kaiser's flag But I know it's a hopeless battle since Ted got his motor-bike

* * *

As we had been given the tickets, my wife and I were determined to visit the flower show I hurried through my morning clinic and we set off Our enthusiasm was slightly damped by the half-mile walk from the car park, the crowds of people, and the sultry, thundery weather However, we went straight to the Grand Marquee for Non-competitive Trade Entries and forced ourselves towards the Rose Display by the well-known technique of accusing mythical people behind you of pushing you rudely forwards Hardly had I arrived at my goal and begun to write down the names of next year's purchases when the loud-speaker stopped its "No smoking" requests and said, "Will any doctor in the grand marquee please go to the ambulance tent at once" Reluctantly and with even greater difficulty I forced my way out, and, asking my wife to wait at the marquee entrance, went to the ambulance tent

A very large and elderly lady had collapsed with substernal pain She said that she was subject to heart attacks for which she took tablets, but that, as she had wanted a day off, a really good outing, and a complete change, she had left the tablets at home The St John Ambulance Brigade and I undid her corsets and I applied my ear to the lower part of her sternum Both heart and bowel sounds were loud, clear, regular, and unhurried I straightened my back and considered the next step At this critical moment, to my relief, another, obviously professional, figure entered the tent "Ah, a proper doctor, I see," I said, "I am only an orthopædic surgeon, I am sure this lady will receive better advice from you than from me" "I am sorry, I am only a medical officer of health," was the answer We consulted together and decided that the interests of the majority of those present in the tent would be served best if she was taken by ambulance to the casualty department of the local infirmary

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[1] Report of the Departmental Committee on Proceedings Before Examining Justices Cmd 479 H M Stationery Office, 1958

Needless to say, my wife was no longer at the marquee entrance When we did meet, some time later, it was obviously hopeless to try to enter any of the marquees, so we consoled ourselves with the sundries section By the time I had bought several garden chairs, tables, and other horticultural aids I realised that it had been an expensive consultation

* * *

In these days of highly specialised anæsthesia when it is so easy to attribute difficulty to some misbehaviour of the flowmeter or to some atypical activity at the end-plates, it is strange to look back to the days when the man dozing at the head of the table took some responsibility for things going wrong I shall always look back with pleasure to the day when I worked with a Hibernian anæsthetist who had all the charm of his race If I said "is there a little congestion?", he would promptly reply "Yes, indade, she's absolutely purrrple" Or if I asked "Is she straining a little?", he would reply "Yes, she's as harrd as a boarrd"

* * *

Seated one day at the Dog Show, I was weary and ill at ease until I overheard two ladies discussing their doctors In readiness for the day when such doctor-fanciers hold doctor-shows at which they will walk their favourite practitioners round in a large circle—instead of, as at present, running them round in small ones—I offer a basic classification of the zoological genus *Medicus*

1 *M hocuspocus* (or Quackshund)—a common wild (*non-registered*) species, developed from Barbary corsair blood-lines

2 *M familiaris*—a well-broken species including such types as *M geepee debilitatus* (Bevan) or *M spina professionis*, according to who's talking This type belongs to the great working group of *Medicus* and is of great utilitarian value, being used as draught animals, distributors of susstificates, herders of livestock (which are rounded up with great alacrity), and guide-animals for the socially inadequate *M geepee deb* (Bevan) hunts singly or in small packs, ranging rapidly about a terrain which it most jealously preserves

Good points are long pendulous ears (for meshing with stethoscopes), powerful and free-acting hind legs, long memories, thick skins, and poor appetites Attempts to deepen the purse of this type have been unsuccessful Coats range from hairless to long-haired varieties Common colours are white, livery, puce-magenta, grey grizzled, and tartan These animals prefer fur-bearing well-heeled prey and have the temperament, size, and intelligence to qualify as household pets

Individual breeds of *M familiaris* include *M chirurgus*, a sporting type from retriever blood-lines, pursuing fur- (mink for choice) *bearing* prey *which it flushes out very thoroughly* *M chirurgus* works best in excavations, orifices, and cavities Usual colours are white, white mask with rufous muzzle, prominent abdomen, and alert expression For these animals to kill prey is a disadvantage

And now if you fellow dogsbodies will excuse me I have to see a patient about a condition powder

* * *

"They fool me to the top of my bent" Thus, with Hamlet, must be thinking the ghost of the illustrious Emile Coude His grandnephew, M Hercule Coudé, has done us service in keeping his name to the fore, but, alas, he falls into the popular error of attributing the straight catheter to M Jaques

It is natural to associate catheters with the French, but in this case the catheter is English Its date of origin is unknown, but it was widely used in the 18th century when, for obvious reasons, it was known simply as "the jakes" In the Victorian era feelings against the name ran high, and it was impossible to move in urological circles without becoming involved in heated arguments The climax was reached at a certain meeting when it was decided to consign the jakes to oblivion This so affected a French visitor that he leapt to his feet with the now famous ejaculation "Eurethra!" Called to the rostrum, this man, M Jaques, gave an impassioned speech in which he implored the audience to consider the patient before any matter of prudery He saved the day, and since then the spelling of the catheter has been "Jaques"

Letters to the Editor

CHILDREN IN HOSPITAL

SIR,—If a child is suddenly whisked away from home with, say, acute appendicitis, daily visiting is undoubtedly a great advantage The patient is likely to be ill and in pain and everything happens too quickly for him to be able to adjust himself Not so in a long-term hospital Here the patient's stay is of many weeks or months, he has time to reorientate himself and learns to make the hospital his temporary home Patients in such hospitals are always drawn from a wide area and visiting is expensive both in time and in money

Because the patients are usually well and because they are in hospital a long time, orthopædic hospitals have always been cheerful and rather unconventional places At this hospital there are school lessons and cinema shows, birthday teas on the lawn, and a Boy Scout troop, and the child feels that he is a member of a community much, I suppose, as a child who has been sent to boarding school

All this has been pointed out before, and in a number of long-stay hospitals with whom I have been in touch the introduction of frequent visiting has been resisted by the senior staff Yet, because of the propaganda by psychiatrists and psychiatrically minded pædiatricians, the Ministry of Health has more or less forced us to increase visiting from one to three days per week, and pressure is now being exerted to introduce daily visiting

This propaganda is being backed up by a film *A Two-year-old Goes to Hospital* I am unimpressed by it as a serious argument in a serious discussion Ever since the days of Al Jolson, audiences have been moved to tears by the pathetic appearance of a small child looking sadly through the bars of a cot Only then, if I remember rightly, the child was looking accusingly not at an ogre of a Matron but at Daddy who was not visiting Sonny Boy any longer because he and Mummy could not get on together Let me be careful in what I say If on the day of admission and under the immediate impact of the separation we asked our mothers whether they wanted daily visiting or not, a number would probably opt for it But soon they find to their amazement that the children are settling down perfectly well It is a tragedy to develop a tuberculous hip, but, properly handled, even a boy of five can adjust himself to such a situation, can understand that he is in hospital because he has a poorly leg and that his mother will visit him on Sunday Again, let me admit that there are exceptions and it is the child of 18 months or so who is most likely to find difficulties This is the awkward age when one is old enough to worry about one's surroundings but not quite old enough to understand Recently we had such a little girl in with poliomyelitis, she settled badly, was bewildered and withdrawn Because she was difficult I arranged for the mother to call in every day, to go with the child to the massage department, to sit by the bed side when I did my ward rounds The response was good, and when the mother called on me a fortnight later we agreed that things had improved a good deal The question she then asked me was typical Not "I hope you will nevertheless not withdraw the privilege of daily visiting", but "do I still have to come every day ?"

When the three visiting days per week were introduced at this hospital I wrote a circular letter to the parents which was handed out on a certain Sunday afternoon at 2 o'clock At 2 10 there was a knock at the office door and one of the sisters asked me to come to her ward "There is almost a riot on, Sir" was the report I went and found myself surrounded by mothers who wanted to know what "all this is about" They asked when were they to do their *shopping*? Who, they wondered, was going to get the tea ready for their husbands coming home from work? I told them that this was only a permission to visit, that they did not *have* to come every time if they were busy, but they looked through that argument at once If there was no visiting, they said, their child would not miss them, but if there was he would feel neglected unless they came. And so they come, or arrange for Granny to come, and even pay neighbours to visit their child so that he should not feel neglected on visiting day Travelling as much as three hours here, and three hours back, summer and winter, for months and months

However this question goes further It has been said by psychiatrists that the separation of a child from his mother causes severe, lasting psychological damage That there is a direct connection between it and such things as juvenile delinquency, and long-stay orthopædic hospitals have been singled out for blame in this matter This is not our experience at all Orthopædic surgeons who work with these crippled children find that they grow up into perfectly well adjusted adults and good citizens In the ordinary run of fracture-clinic patients they stand out because of their quiet, non-complaining behaviour Far from being bitter their suffering has made them considerate of others Dare one suggest that sometimes difficulties, properly met, ennoble the character?

Permit me, Sir, to end with a letter I received a few days ago from a farmer's wife in Derbyshire. It concerns a boy of 6 who had poliomyelitis and who is to come into hospital for an operation

"Dear Doctor, I am sorry to say John's sister broke-out in German Measles today, there is only John who has not had them now So all being well I will write again on the 26th of August and let you know how things are. John is very disappointed he is unable to come to the hospital yet, as he is looking forward to coming very much I, John's mother, had German Measles three weeks ago Yours truly Mrs X."

King Edward VII Orthopædic Hospital,
Sheffield
E G HERZOG

SIR,—Professor Illingworth's thoughtful lecture (July 26) and your own forthright leading article have evoked replies which by their vehemence cloud the main issues and exaggerate the minor ones

No one will deny that the larger infectious-diseases hospitals situated in and serving a heavily populated area provide an essential and efficient infectious-diseases service

A different picture is presented by many of the smaller infectious-diseases hospitals, some of which do not have a resident medical officer, and where clinical-laboratory and radiological facilities are absent or rudimentary Admissions are sometimes accepted by nursing staff or even clerks The term "infectious" is interpreted in its widest sense A consultant in infectious diseases, at his main hospital 15-20 miles away, cannot hope to provide adequate supervision of urgent cases

A clinical laboratory is as essential in the treatment of meningitis as an operating-theatre is in the treatment of acute appendicitis No-one would consider admitting a case of appendicitis to a hospital without a theatre constantly staffed Cases of meningitis are admitted to these small infectious-diseases hospitals with little or no laboratory facilities

The Ministry's approach to this important matter is difficult to understand They have suggested, and it is widely accepted, that infectious blocks should be included within the curtilage of all new general hospitals The present central infectious hospitals would, of course, continue to provide for local needs and for cases from further afield which, because of their complexity or epidemiological character, require the specialised skill and equipment only available at such hospitals It comes, therefore, as a surprise to learn that the plans for the new Huddersfield General Hospital of 600 beds, one of the first in the country, do not provide for an infectious block This would seem to be a retrograde step, more especially as it may create a precedent

Dr Breen (Aug 16) is seriously misinformed when he states that pædiatricians "have wrought so well as to imperil their own survival" He presumably bases this statement on the prevalent misconception that the amount of work done in a specialty depends on the number of beds allocated A careful analysis of the figures will show, broadly speaking, that in those areas where the number of pædiatric beds has fallen by a half over the past five to ten years, the number of outpatients have practically doubled It is generally accepted that outpatients are by far the most responsible and onerous part of a physician's work, a burden that the infectious-diseases consultant is very largely spared New pædiatric appointments are being made and old appointments split It is noteworthy that between 1934 and 1956 in the U S A the number of pædiatricians has quadrupled, while in the same time the total of physicians has increased by only a third Such an increase is exceptional, but the trend is obvious in other countries as well.

Halifax General Hospital
W P SWEETNAM

SIR,—Professor Illingworth's lecture and your leading article raise a number of points involving fever hospitals

These hospitals have long since discontinued routine admission of uncomplicated scarlet fever and measles On the other hand, pneumonia is a notifiable infectious disease, while "meningitis" may include a variety of conditions, some notifiable such as cerebrospinal fever and, sometimes, poliomyelitis It is therefore both logical and safer to send these cases to fever hospitals, whose senior consultants, incidentally, have an unrivalled experience of these infections—not to mention gastroenteritis

Professor Illingworth decries the efficacy of cubicles in the prevention of cross-infection, and while this may in some instances be true—gastroenteritis due to *Escherichia coli*, for example—the successful segregation of all types of infectious diseases alongside each other has been carried out for years in fever hospitals The reason for trouble in other types of hospital, even with cubicles, may well be failure to apply efficiently the approved techniques of fever nursing—a potent argument for the retention of this particular training

Undoubtedly, many pædiatricians have had extensive experience of infectious diseases, but this can hardly be universal There is surely some arrogance in claims that the age of the patient rather than the physician's experience of the diseases concerned should determine who is to look after him If pædiatricians are so anxious to assume control of infectious diseases, they should at least make it compulsory for their trainees to serve an apprenticeship, preferably as residents in fever hospitals

An alternative solution for the main fever hospitals, which had the blessing of the Royal College of Physicians, is that they should be run by general physicians with a primary interest in infectious diseases This is in practice very frequently the case, in fact if not in name Surplus beds, if any, can then more easily be devoted to general medicine rather than pædiatrics, and staffed where necessary with the help of outside consultants These beds could readily be switched back to fevers in the event of an epidemic The continuity of medical administration, inseparable from fever practice, still intimately linked with the public-health service and based on long experience, would be preserved. The disruption of attached special units, such as those for poliomyelitis or tuberculous meningitis, into separate age-categories, a process wasteful of medical experience and efficiency, as well as of physical resources and money, would be avoided

Have the pædiatricians given due thought to the public-health aspects of the case, and to what medical officers of health think?

Hoylake, Cheshire J L FLUKER

SIR,—Since the publication of Dr Lawson's letter (Aug 23), I have heard from Mr A G Linfield, chairman of the South West Metropolitan Regional Hospital Board, and I gladly accept his assurance that it was not his intention, at the interview which we had, together with Major-General Hawes, on July 23, to convey to me the impression that the board were in any way committed by *the Ministry's suggestion to close Queen Mary's as a* general children's hospital

Queen Mary's
Hospital for Children,
Carshalton, Surrey

H J WELLS
Chairman of Management Committee

APPROVED NAMES

SIR,—The interim report of the Committee on Cost of Prescribing contains various criticisms of the approved names which the General Medical Council publishes on the advice of the British Pharmacopœia Commission The commission was not advised by the committee that it proposed to discuss approved names, but had this intention been known the commission would have wished to furnish evidence for the committee's information, thereby avoiding the many inaccuracies which appear in the report The commission regrets that they were not invited to appear before the committee

The commission now offers the following observations on some of the statements which appear in the report

1 The report states (para 41) "There are for example just under 5000 *proprietary preparations available for prescribing* Economies would follow, we believe, if simple approved names *for new products could be evolved quickly* and given the widest possible publicity"

In the majority of cases the provision of an approved name has no effect on the price of preparations The issue of the simple approved name primidone for the product 'Mysoline' has had no effect on the price of the drug—to quote only one of numerous possible examples

2 *The committee states in* para 42 of the report that "We are informed, for example, that the present rules of nomenclature require that the approved name should be based on a drug's chemical constitution"

This statement is erroneous The guiding principles used in selecting or devising approved names do not impose an inflexible style and it will be seen that many names are not based on the drug's chemical constitution—e g, most antibiotics, warfarin, azovan blue, gallamine, lignocaine, macrogol, mustine, sulphan blue Among these guiding principles are the following

> "An attempt should first be made to form a name by the combination of letters or syllables from the systematic chemical name
>
> Cognisance should be taken of the names of closely related substances and where desirable the name should reflect this relationship
>
> The names should be distinctive in sound and spelling and should not be liable to confusion with names already in use
>
> Names which are difficult to pronounce or remember should be avoided
>
> Names used in the *United States Pharmacopœia*, *New and Nonofficial Remedies* (Drugs), and international non-proprietary names should receive preferential consideration"

In giving preferential consideration to existing non-proprietary names, and so avoiding the international *confusion which* may arise if a second name is adopted for the same drug, the commission has found it preferable *in some instances to accept* such a name in spite of its defects For example, the names chlorotrianisene, diphenylpyraline, and tripelennamine were issued by the American Medical Association and widely used before the drugs were sold in Britain Although the commission was critical of these names, the balance of advantage lay in accepting them as approved names

3 The report states (para 43) that "At present a year or two may elapse before an approved name is formulated for a new drug During this period doctors get into the habit of prescribing the new preparations by their trade names "

It is exceptional for a long period to elapse between the appearance of a new drug on the English market and the publication of an approved name Approved names for new drugs of English origin are usually available by the time the drug is placed on sale and indeed the approved name is generally available before the drug is distributed

During the past five years, nearly 60,000 copies of lists of approved names have been circulated by the commission, but *wide advertisement is the most potent factor in establishing* the names of medicinal products and it is manifestly not a function of the commission to advertise approved names in the manner or on the scale adopted for trade names Copies of supplementary lists of approved names are supplied to some hundreds of correspondents at home and abroad and they are published in many professional journals

4 The committee states in para 46 of its report that "We consider also that before putting a new drug on the market manufacturers should be encouraged to ask the British Pharmacopœia Commission to give it an approved name As soon as that has been done the approved name should appear on labels and advertising literature for proprietary preparations as prominently as the trade one"

Over many years it has been the practice of most British manufacturers to approach the commission for an approved name for a new drug before placing it on the market For such products the approved name is usually available whilst the substance is undergoing trials and before it is generally released for sale The commission has no control over the manner in which approved names are used by *manufacturers* on labels and in advertising literature

5 The committee expresses the opinion (para 44) that "some of the principles of nomenclature now in force may well be inappropriate today", and recommends that the commission be asked to review these principles It is difficult to comply with this request unless a more specific statement is provided

The report makes no reference to a number of important considerations that apply in the selection of approved names, such as the international aspects including the non-proprietary names issued by the World Health Organisation, and by the American Medical Association for many drugs that appear in England only after a period of use in the United States Indeed most drugs introduced on the English market have had a period of use in the United States or elsewhere in association with a non-proprietary name, and unless over-riding considerations apply it is undesirable to coin a second non-proprietary name even when the established name falls short of the commission's desideratum Approved names are applied not only, *and perhaps not primarily*, in the writing of prescriptions but also in scientific articles appearing in journals with world-wide readership, *for reference purposes*, and in the labelling of products in accordance with legal requirements including purchase-tax and poisons regulations Approved names are also of great value in indicating to prescribers and pharmacists that the same drug is being described under more than one trade name

Attention is also drawn to the problems which arise in relation to existing names especially those registered as trade marks. It has been a frequent experience that a proposal for what would appear to be an admirable short name must be discarded in favour of a more complicated one because, on the authoritative advice received by the commission from the Patent Office, the short name is held to conflict with a trade mark registered in this country.

The commission offers this statement in the hope that it may dispel any misunderstanding which the report may have created, and that it may help towards a better appreciation of the origins and purposes of approved names.

General Medical Council Office,
44, Hallam Street,
London, W.1.

D. M. DUNLOP
Chairman, British Pharmacopœia Commission 1953-1958.

T. C. DENSTON
Secretary.

MIDGET ANÆSTHETIC MACHINES

SIR,—In your annotation of Aug. 16 you draw attention to the development of two midget anæsthetic machines which depend on a non-explosive cyclopropane mixture to give but a few minutes' anæsthesia.

I have long felt that there might be a place for a really portable apparatus capable of producing anæsthesia of one to two hours' duration, for possible use in the Services, major disasters, industrial accidents, shipping and air lines, &c., and with this end in view I have adapted an existing lightweight oxygen therapy unit into a halothane/oxygen closed-circuit anæsthetic machine with various refillable or "throw-away" components. This apparatus is still in process of manufacture, testing, and calibration.

Southlands Hospital,
Shoreham-by-Sea.

P. J. C. BURTON.

ANATOMY OF THE CARDIA

SIR,—Some of the conclusions endorsed in your leading article of Aug. 16 are still controversial.

In particular, the opinion of Atkinson et al.[1] that a raised pressure zone in the lower œsophagus immediately above a hiatus hernia signifies the activity of a "sphincteric barrier" is open to criticism. Jennings[2] in his review of this paper has already pointed out that in such cases the recording tube, as a foreign body, might well cause sustained contractions of the lower œsophagus.

Undoubtedly the œsophagus immediately above the œsophagogastric junction exhibits particular properties of distensibility and contraction, sufficient to be designated the "gastroœsophageal segment of expulsion" by Lerche,[3] but this does not necessarily imply that it serves to prevent reflux. It may chiefly be concerned with forward propulsion after swallowing, by contraction of the segment as a whole, analogous to the distal pyloric antrum.

Several investigators have mentioned the apparent weakness of this "pressure barrier".[4–6] Wolf et al. believe that the terminal œsophageal segment is so easily ballooned out that it constitutes part of the hernial pouch, the junction appearing in cineradiographs as a shallow horizontal groove. Actual invagination of the distal œsophagus in hiatus hernia has been reported by Kleinfelter.[7]

The area from which Atkinson et al.'s pressure recordings were taken, therefore, may have been the distal 1-3 cm. of the "tubular" œsophagus and not the most distal segment. In radiographs this former region often appears narrowed for several centimetres, and it may be more irritable than normal because of œsophagitis.

The observation that delay in passage of barium through the œsophagogastric junction can be abolished by continuous drinking of barium, as distinct from individual swallows, does not prove that they are different physiological processes, as Creamer and Pierce would have us believe. The build-up of pressure by rapid passage of a heavy liquid such as barium might be sufficient to obliterate this weak "sphincter" zone.

In spite of the inability of Atkinson et al. to demonstrate a change of pressure where the hernial neck passes through the hiatus, the fact remains that in a large proportion of cases the radiologist is unable to fill the hernia by reflux from the stomach (Flood and Hennig,[8] for example, report reflux in 31 out of 70 cases, many having repeated examinations.) Wolf et al. observe that the site at which reflux is most often obstructed is at the level of the hiatus—i.e., the mechanism is extrinsic. Presumably this functions effectively during the examination and at other times, but at night, particularly when a low tone in the crus combines with the supine position, reflex occurs.

In my limited radiological experience I have found no correlation between the presence or absence of reflux symptoms and the extent to which radiological reflux takes place—i.e., whether only the hernial pouch is filled or the whole œsophagus.

Southmead Hospital,
Westbury-on-Trym, Bristol.

E. A. W. HOUGHTON.

HÆMOPHILIA-LIKE STATES IN GIRLS

SIR,—Dr. C. Merskey (Aug. 2) has commented on the omission in our paper[9] of the family first reported by Treves[10] in 1886 and re-studied by him in 1950.[11] This family was not discussed because of the atypical hereditary pattern.

In the first four generations the disease was reported to have been transmitted from father to son, which does not occur in classical hæmophilia. We, of course, cannot judge the validity of these early reports. We were impressed by the apparent severity of the bleeding state in the members of this family, despite the fact that their clotting-times were only slightly prolonged. In both true hæmophilia and Christmas disease, it is uncommon to find permanent ankylosis of joints in patients whose clotting-times are only one or two minutes above normal.

The unequivocal diagnosis of classical hæmophilia can only be made if the typical hereditary pattern is obtainable, if the bleeding and prothrombin times are normal, and if the absence of the specific factor, thromboplastinogen (antihæmophilic globulin), can be established with certainty. The coagulation defect of the girl we reported is, according to all the tests now available, identical with that of true hæmophilia, nevertheless, the diagnosis of classical hæmophilia cannot be made because of the absence of a hereditary history. The bleeding condition in one of a pair of identical twins which Dr. Conway and I reported[12] also corresponded closely to classical hæmophilia, but again the diagnosis could not be made with certainty because of the atypical hereditary pattern.

The question arises as to what determines the basis for applying the term "hæmophilia". If it is the characteristic hereditary pattern, then Christmas disease or P.T.C. deficiency can justifiably be called hæmophilia B. If,

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1. Atkinson, M., Edwards, D. A. W., Honour, S. J., Rowlands, E. N. *Lancet*, 1957, ii, 1138.
2. Jennings, D. *Abstr. World Med.* 1958, 23, 426.
3. Lerche, W. The Esophagus and Pharynx in Action. Springfield, Ill. 1953.
4. Adler, H., Fernie, C. N., Lanigan, J. M. *Surgery*, 1958, 44, 63.
5. Creamer, B., Pierce, J. W. *Lancet*, 1957, ii, 1307.
6. Wolf, B. S., Marshak, R. H., Som, M. L., Brahms, S. A., Greenberg, E. I. *J. Mt Sinai Hosp.* 1958, 2, 167.
7. Kleinfelter, E. *Radiology*, 1956, 57, 562.
8. Flood, C. A., Hennig, G. C. *Gastroenterology*, 1958, 35, 62.
9. Quick, A. J., Hussey, C. V. *Lancet*, 1958, i, 1294.
10. Treves, F. *ibid.* 1886, ii, 533.
11. Merskey, C. *Quart. J. Med.* 1950, 20, 299.
12. Quick, A. J., Conway, J. P. *Amer. J. Med.* 1949, 7, 841.

however, it is the lack of thromboplastinogen which determines the name, the term hæmophilia B is illogical, but angiohæmophilia or vascular hæmophilia would be a suitable name for the disease in which the thromboplastinogen is *deficient* and the *bleeding-time* is prolonged Pseudohæmophilia would be the preferred name, however, if hæmophilia designates the hereditary pattern

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ARMAND J. QUICK

COUDÉ STRAIGHTENED OUT

SIR,—As the author of the article on Coudé mentioned by Mr Hamilton Bailey and others (Aug 23), I feel that to call the article a " deception " or " hoax " is unfair None of the Cardiff students did anything to bring the article to the attention of anyone connected with *A Short Practice of Surgery* Coudé is something of a standing joke in Cardiff, and nobody really believed in him

I have not yet given up all hope of revising our knowledge of medical history I am now doing some research about Pyogenes, an Ancient Greek who postulated the existence of the staphylococcus many years before the microscope was invented I hope that before long he will achieve his fair share of fame, in the form of a footnote in our most popular textbook on bacteriology

Morriston Hospital,
Swansea.
RAPHAEL PASH

THE WAALER-ROSE FACTOR IN RHEUMATOID ARTHRITIS

SIR,—I have not been able to satisfy myself that my arthritic patients will be helped by the knowledge that their serum may potentiate the agglutination of sheep cells sensitised with rabbit amboceptor [1] I shall comfort myself with the words of Broussais [2] " Facts which cannot be used for healing do not belong to the physician, they belong to the naturalist " This test is based on the gospel that rheumatoid arthritis is an entity, separate and distinct from all other diseases But Clifford Allbutt [3] said in 1866 " We are now but awakening from the metaphysical delusion that diseases are separate entities " Poynton [4] wrote of the rheumatic disorders as " allied disorders [with] strange likenesses as well as strange differences For the student it is easier and more helpful to define differences, but for the expert it is often of service to study similarities "

In our present state of ignorance of its causation, such terms as rheumatoid arthritis can only be tentative A word like " rheumatoid " can be used as we use " carcinoma " to signify a real change in the tissues Then it must be applicable to monoarthritis and the infective forms of arthritis as well as to polyarthritis Or we can use rheumatoid in its popular sense, as a convenient term like scrofula and dropsy It is purely tentative and at the next advance in knowledge may be swept away At present there is a danger that knowledge be suppressed by insisting too much on a " diagnosis " as the basis for the discussion of any rheumatic patient's symptoms

Not one of the fifty or so extant classifications of rheumatism can include more than 60% of all cases [5] [6] Cobb [7] was unable to fit more than one-eighth of 372 rheumatic patients comfortably into any of the standard categories Mainland [8] has also shown how unworkable are all attempts to classify rheumatism

Much of the present confusion in rheumatology is due to superstitious belief in the ancient terms, acute and chronic, and has arisen because our desire to classify has outrun our knowledge If we are guided by superficial appearances only, we shall be like the two boys who were asked to grade a sack of apples Not knowing that there existed real differences between the apples (Rome Beauties, Jonathans, &c), one graded his half into large apples and small apples, while the other also had two heaps, red apples and green apples Needless to say, in both lots there were many intermediate and unclassifiable types

Melbourne
MICHAEL KELLY.

SHOULD BIBLIOGRAPHIES GIVE TITLES OF PAPERS?

SIR,—Dr Max Millard (Aug 16) suggests that *The Lancet* make the gesture—how he cannot suggest May I propose this gesture which would help and cost little extra space adding the concluding page of all articles quoted?

Wyke House Hospital,
Isleworth, Middlesex
H PULLAR-STRECKER

TOBACCO AMBLYOPIA

SIR,—The interesting article by Dr Heaton and his colleagues in your issue of Aug 9 mentions the low serum-vitamin-B_{12} levels in vegans, who, because they consume no animal food, tend to develop a dietary deficiency of vitamin B_{12} and therefore may provide valuable information on this subject

My colleagues and I in our investigations on vegan non-smokers have found their low serum-B_{12} levels to be associated with an increased urinary excretion of thiocyanate [1] which could be reduced by oral or parenteral administration of vitamin B_{12} [2] In a communication [3] to the Fourth International Congress of Biochemistry in Vienna, we propose to show that in non-vegan smokers there is also an increase in the urinary excretion of thiocyanate roughly proportional to the degree of smoking and parallel with the increase in serum-thiocyanate recently found by Stoa [4] in smokers This increase in thiocyanate excretion may occur also in " stress " conditions such as menstruation, pregnancy, or lactation *when there is an increased requirement* for vitamin B_{12} It may have a bearing on the suggestion of Heaton et al that the beneficial effects of vitamin B_{12} on tobacco amblyopia are due to its making good a *deficient* intake of the vitamin Vegans who are subject to such a deficiency are usually non-smokers However " eye trouble ", which is now being investigated, has been encountered in a life vegetarian (living on an almost vegan diet) after she had *voluntarily taken up extensive smoking for some time*, and greatly increased her urinary excretion of thiocyanate

Thiocyanate is formed in the body by the action of the liver enzyme rhodanese on cyanide [5] After administration of ^{14}C-labelled cyanide to dogs most of the radioactivity has appeared as $S^{14}CN$ in the urine [6] It therefore seems logical to assume that an increase in thiocyanate excretion during smoking would be caused by any cyanide derived from the tobacco Tobacco smoke has been shown to contain cyanide in amounts of the order to be expected if the increase of 5–20 mg in the daily thiocyanate excretion in smokers were due to cyanide inhaled in the tobacco smoke [7]

These findings indicate that it would be of interest to study the cyanide and thiocyanate metabolism in tobacco amblyopia

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1 *Lancet*, 1958, i, 1216
2 Broussais, cited by Horder T *ibid*, 1948, ii, 715
3 Rolleston H D Life of Sir Clifford Allbutt London, 1929
4 Poynton F J *J State Med* 1936, 44 349
5 Stone K *Postgrad med J* 1942, 18, 5
6 Robinson, W D , et al *Ann intern Med* 1953, 39, 497
7 Cobb, S , Merchant, W R , Warren J E *J chron Dis* 1955, 2, 50
8 Mainland, D *Ann rheum Dis* 1955, 14, 337

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1 Wokes, F , Badenoch, J , Sinclair, H M *Voeding*, 1955, 16, 590, *Amer J clin Nutr* 1955, 3, 375
2. Wokes, F Picard, C W , Paper read to Third International Congress of Biochemistry, Brussels 1955
3 Wokes, F , Hytten F Paper to be read to Fourth International Congress of Biochemistry Vienna 1958
4 Stoa, K F Studies on Thiocyanate in Serum University of Bergen, 1957
5 Lang, K *Biochem Z* 1933, 262, 14
6 Boxer, G E , Rickards J C *Arch Biochem Biophys* 1952 39 ~
7 Osborne, J S , Adamek, S , Hobbs, M L *Anal Chem* 1956, 28, 211

There might be expected to be a high rate of urinary excretion of thiocyanate, which would be decreased by administration of vitamin B_{12}, and the rate of decrease might perhaps be compared with the clinical improvement as measured, for example, by visual acuity. Should this occur, a useful biochemical method might emerge of studying the development and treatment of this disease.

The action of the vitamin may be better understood if it be pictured as existing in the body largely in the form of hydroxocobalamin, which can absorb cyanide very readily to form cyanocobalamin. The latter could then take part in essential metabolic processes involving the use of cyanide as a brake on respiratory enzymes such as cytochrome oxidase. Based on these theories, a hypothesis[8] has been put forward regarding a possible role of vitamin B_{12} in human nutrition, involving its participation in the synthesis of methionine. This is one of the sulphur-containing aminoacids in the lens of the eye in which main interest has long been centred.[9] In the metabolism of the lens cytochrome oxidase, which plays an important part, is inhibited by cyanide, which may function as a necessary brake on the activity of the enzyme and thus be indeed an essential metabolite. The rate of excretion of minute traces of cyanide in the breath of normal subjects has been found to be related to the basal metabolism, indicating that the cyanide is taking part in general metabolic processes.[10]

These theoretical aspects may provide a basis for the practical treatment or prevention of tobacco amblyopia by administration of vitamin B_{12}, preferably orally, in frequent small doses, supplemented perhaps with thiamine and other B vitamins. Study of the cyanide-thiocyanate metabolism (e.g., by estimation of serum-thiocyanate or of urinary thiocyanate excretion) might be helpful.

King's Langley, Herts. **FRANK WOKES.**

SIR,—I was very interested in the article by Dr. Heaton and his colleagues. I should like to comment on the suggestion that the nutritional retrobulbar neuritis of prisoners of war may be due to a combined deficiency of vitamins B_1 and B_{12}.

In West Africa, some of my most extended trials were done with autoclaved 'Marmite'. This was a follow-up of the work of Landor and Pallister[11] at Changi Civil Prison, Malaya, who had demonstrated that autoclaved marmite would cure the skin lesions of what is recognised today as "ariboflavinosis", as would ordinary marmite, which I had been using. There was also strong presumptive evidence of a similar effect on vision.

While autoclaved marmite produced dramatic cures of the more visible lesions, including keratitis, confirmative evidence about neurological lesions required months of observation and careful selection of cases. Only those with a very recent history of nutritional retrobulbar neuritis could be selected, for within a few months irreversible changes would occur and a known effective treatment could not be long withheld. I found nutritional retrobulbar neuritis responded as well to autoclaved marmite as ordinary marmite.

Beriberi was a rare disease in Southern Nigeria where the staple carbohydrates were different from the Far East, and rice a "luxury". I saw no evidence of it, clinically, in any patient.

The discovery of ariboflavinosis cleared any doubts about the oral and skin lesions, formerly held to be "pellagrous" (though by 1938 nicotinic acid had been virtually excluded). But any coexistent neurological condition remained obscure. My own belief is that marmite contains that "something else", still unknown, which is both a protective and curative factor. Against riboflavine affecting neurological conditions is the absence of experimental proof. As long ago as 1940 V. P. Sydenstricker told me that neither he nor his colleagues had been able to find any evidence of retrobulbar neuritis in their cases of ariboflavinosis.

Vitamin B_{12} has always offered a possible link-up with these problems and has been a logical consideration for follow-up ever since its discovery. So far as I know the only such trial has been that of J. H. Walters in Arabia. In a personal communication (1953) he informed me of its success in cases of recent origin of a nutritional ataxic syndrome. This condition however, appeared to be separate from nutritional retrobulbar neuritis as in none of his cases was there any evidence of this.

It may well be there is more than one type of dietetically produced "cord" syndrome. Pallister[12] described an ataxic paraplegia in Chinese Malays which was not associated with a retrobulbar neuritis.

Finally, almost all P.O.W./F.E. medical officers state that nutritional retrobulbar neuritis is not caused by vitamin B_1 deficiency. Denny-Brown[13] and Spillane,[14] both of whom conducted exhaustive surveys of nutritional neurological conditions in Service personnel, said the same.

Nutritional retrobulbar neuritis is a true deficiency disease. While much can be definitely excluded, its exact cause remains unknown.

Parkstone, Dorset. **D. FITZGERALD MOORE.**

LECTURES ON TAPE

SIR,—We read with interest Dr. Oakley's letter (Aug. 23) in which he mentions our suggestions for a library of medical tape-recordings. He, and others, may like to know that, although our original ideas have been greatly modified, they have developed into the Medical Recording Service of the College of General Practitioners, which has for some months now been issuing talks on tape and long-play gramophone records to members of the College.

JOHN GRAVES
Chelmsford, Essex. **VALERIE GRAVES.**

TREATMENT OF NEPHROTIC SYNDROME WITH CHLOROQUINE

SIR,—The usefulness of adrenal corticoid therapy in treatment of the nephrotic syndrome is well documented and has been recently reviewed.[15] Dr. M. Plaza de los Reyes (July 19) reports good results following the administration of 0·75 to 1·0 g. chloroquine diphosphate for 2 to 4 months to three patients with "the nephrotic type of chronic nephritis". Our own experience with chloroquine therapy in three adults and four children with idiopathic nephrotic syndrome has been disappointing.

The children received at least 0·25 g. and the adults 0·75 g. chloroquine diphosphate for 2–3 weeks. The hydroxy-ethyl amino analogue of chloroquine was administered to two children. A complete remission occurred in one child and proteinuria decreased in two adults. However, no improvement occurred in the other four patients, although subsequent corticoid therapy produced complete remission (disappearance of proteinuria) in all of them. Thus, in our experience with somewhat smaller dosage and shorter courses than those employed by Dr. Plaza de los Reyes, chloroquine therapy has been far less effective than corticoid therapy in the treatment of idiopathic nephrotic syndrome.

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HOWARD C. GOODMAN
JAMES H. BAXTER.

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[8] Wokes, F., Picard, C. W. *Amer. J. clin. Nutr.* 1955, 3, 383.
[9] Pirie, A., van Heyningen, R. Biochemistry of the Eye. Oxford, 1956.
[10] Boxer, G. E. Private communication.
[11] Landor, J. V., Pallister, R. A. *Trans. R. Soc. trop. Med. Hyg.* 1935, 29, 121.
[12] Pallister, R. A. *ibid.* 1940, 34, 203.
[13] Denny-Brown, D. *Medicine,* 1947, 26, 41.
[14] Spillane, J. D. Nutritional Disorders of the Nervous System. Edinburgh, 1947.
[15] Goodman, H. C., Baxter, J. H. *Metabolism,* 1958, 7, 40.

"LIVER FUNCTION"

SIR,—The references in your leader of Aug 23 to fractional determination of bilirubin pigments may be regarded as misleading, even when allowance is made for brevity

Firstly, it is not clear whether by fractional determinations is meant chromatographic separation by one of the methods of Lathe and his coworkers, or the more familiar one-minute and total bilirubin levels which have been advocated by Watson and others [1,2] In either case the implication that the method has yet to be used as a test of liver function is misleading Results obtained with the chromatographic method in the differential diagnosis of regurgitation jaundice [3,4] have been disappointing since there is considerable overlap in the patterns found in hepatitis, in extrahepatic biliary obstruction, and in jaundice due to malignant metastases Neither of the reported studies can be regarded as exhaustive, yet it is my opinion that in the differential diagnosis of jaundice chromatographic separation of the serum bile pigments gives no useful information that cannot be obtained more simply by a total bilirubin estimation with specific attention to the type of van den Bergh reaction, and the performance of a simple but sensitive test for bilirubin pigments in urine Your more optimistic attitude may be justified if a method can be found to separate and estimate the bilirubin pigments without preliminary precipitation of the plasma-proteins

It is wrong to suggest that fractional determination of bilirubin pigments is a necessary investigation in the differentiation of the two rare conditions known as the Dubin-Johnson syndrome [5,6] and Gilbert's disease In Gilbert's disease the van den Bergh reaction is negative and bilirubinuria absent in the Dubin-Johnson syndrome the reaction is positive and bilirubinuria is usual More complex methods give results in accord with these simpler observations but are no more certain Where the total concentration of bilirubin pigments is less than 3 mg per 100 ml, as it commonly is in these two conditions, chromatographic separation may be impossible or inaccurate

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A G BAIKIE

HAZARDS OF CHLOROTHIAZIDE THERAPY

SIR,—The warning of Professor Rosenheim and Dr Ross (July 26) is timely Apart from the cases they mention there is another group of patients who may respond well to the drug but in whom unexpected hazards may arise as a result of its use I refer to those patients with hepatic cirrhosis with ascites and œdema who may have a most satisfactory diuresis on chlorothiazide with initial relief of symptoms In these cases the danger appears to be that hypokalæmia may occur and precipitate the onset of hepatic failure and even hepatic coma, as occurred in a case I observed

A man of 62, who was known to have had cirrhosis of the liver for several years, was admitted with ascites and gross œdema There was considerable diuresis on chlorothiazide therapy which was measured by a fall in weight from 238 lb to 219 lb in ten days After this the patient felt greatly improved, but fourteen days after admission he became restless, tremulous, and confused and obviously on the verge of hepatic coma into which he passed in twelve hours At the time these symptoms began the serum-potassium was 4 5 mEq per litre, but even after the chlorothiazide had been withdrawn the level continued to fall, the lowest figure being 2 9 mEq Intravenous therapy with 20% glucose solution and added potassium chloride resulted in his recovering consciousness although he unfortunately relapsed two weeks later and died

The only obvious precipitating cause of the hepatic coma was the lowered serum-potassium level, so that in cases such as this it seems as important to combin potassium chloride therapy as in cases of cardiac œdem treated with this diuretic

London, W 1

JOHN LISTER

INDUSTRIAL MEDICINE AND GENERAL PRACTICE

SIR,—In a leading article in *The Times* of Aug 4, the contention of Dr Stephen Taylor (now Lor Taylor) that "a large part of Industrial Medicine i neither more nor less than General Practice " i quoted, with approval, and on this basis a case is built up for the development of industrial medicine along thes lines Of course, Lord Taylor is entitled to his opinion but as is well known this was not the view expressed in the report of the Committee of Enquiry on Industrial Health Services (the Dale Committee) The true function of industrial medicine, of course, is to advise management, and to suggest that it is just a form of general practice can only do harm by misleading both physicians and industrialists The fact is that there is really no place at all within the factory for general practice, which should be undertaken by the proper person, who is the family physician, any other arrangement will only undermine his authority to the patient's disadvantage In any case, the industrial physician should have something better to do than to seek to duplicate facilities already available through the National Health Service This is not to say that the family physician has no part to play in an industrial medical service, but it is not that of general practice

Medical Department,
The Butterley Co Ltd,
Ripley, Derby

G F KEATINGE

VAGOTOMY IN HYPERTROPHIC PULMONARY OSTEOARTHROPATHY ASSOCIATED WITH BRONCHIAL CARCINOMA

SIR,—Mr Huckstep and Dr Bodkin, in their interesting article of Aug 16, report regression of bilateral gynæcomastia after vagotomy in a case of inoperable bronchial carcinoma I would like to record a similar experience

A man, aged 70, was admitted in April, 1958, to Baguley Hospital with carcinoma in the left upper lobe, clubbing of fingers and toes, osteoarthropathy with mild symptoms, and bilateral gynæcomastia which had been present for five months Both breasts were enlarged, firm, pyriform, and slightly tender

A left thoracotomy was carried out by Mr John Dark on May 7 The tumour was found to be extensively invading the chest wall, as a result of this and other considerations it was not possible to remove the tumour The left vagal trunk, below the recurrent laryngeal branch, and the pulmonary branches were divided Biopsy of the left breast was performed The report (Dr T A White) is as follows

"The fibro-fatty tissue contains an abnormal number of breast ductules surrounded by loose periductal stroma which is infiltrated by chronic inflammatory cells Some of the ducts are dilated, many show marked epitheliosis, some papillary outgrowths are present in the lumina, and some ducts are almost filled by hyperplastic epithelium No mitoses are seen in the sections, there is no evidence of extraductal invasion or of carcinoma The appearances are consistent with a diagnosis of gynæcomastia"

Following operation, the gynæcomastia gradually regressed The patient was seen again on Aug 22 Although his condition

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1 Zieve L Hill E, Hanson, M, Falcone, A B, Watson, C J *J Lab clin Med* 1951, 38 446
2 Watson C J *Ann intern Med* 1956 45, 351
3 Billing, B H *J clin Path* 1955, 8, 130
4 Baikie, A G *Scot med J* 1957, 2 359
5 Dubin, I N, Johnson F B *Medicine* 1954, 33, 155
6 Dubin, I N *Amer J Med* 1958, 24 268

is deteriorating, there is now no gynæcomastia and there are no symptoms of osteoarthropathy Although forward curvature of the nails is still present, the pulp volume appears to have decreased, as is shown by longitudinal wrinkles on the finger-pads

Baguley Hospital,
Manchester, 23

LESLIE DOYLE

PLEURAL BIOPSY

SIR,—In your annotation of Aug 23 you mention two American reports on the value of this procedure, based on series of 23 and 31 cases Perhaps you will allow me a little space to give a brief outline of the findings of Dr A C Pollard, Dr M J Purves, and myself Our results will be fully reported in two papers submitted for publication several months ago

We have carried out needle biopsy of the pleura in 200 patients, 152 of whom had a pleural effusion of unknown origin In these 152 cases, biopsy gave the diagnosis in 101 cases 70 were tuberculous and 12 malignant, and 10 were due to acute pyogenic infection only The series contained at most 85 tuberculous pleural effusions 70 were diagnosed on the histological appearances of the biopsy specimen and 3 on the results of pleural-fluid culture, while in 12 cases the diagnosis remained a presumptive one only Of the 70 cases with a positive tuberculous biopsy, confirmation was obtained by a positive pleural-fluid culture in 25

It is clear that pleural biopsy is by far the most reliable diagnostic measure in suspected tuberculous effusions, and is very worth while in all other pleural effusions whose cause is not obvious We estimate that blind needle biopsy can be expected to give the diagnosis in 80% of primary tuberculous pleural effusions, and in more than 60% of malignant effusions Where a strong clinical suspicion of primary tuberculous effusion exists, and needle biopsy is negative, full surgical biopsy of the pleura should be done, a patient should not be condemned to a long course of chemotherapy on presumptive evidence alone, for there can be no doubt that in a number of cases such evidence misleads

Churchill Hospital, Oxford

PAUL MESTITZ

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—I have been following with considerable interest the correspondence on this subject It appears that your correspondents are making an initial assumption open to serious doubt This assumption is that the pain of "lumbago" is due to some change in the actual disc itself Mr Charnley (July 5) put the problem in a nutshell "One of the most surprising things about acute lumbago is that the amount of pain does not seem to be proportional to the amount of organic change visible in the disc", and, later in his letter, "we rarely found convincing protrusions in these cases but what is cogent to the present argument is that the material removed appeared more often to be normal than fibrous and stringy"

The argument about hyperhydration or desiccation as the cause of disc protrusion seems largely to be influenced by the theory that it is a rise in intra-disc tension that causes acute lumbago I submit that there is far too little foundation for this assumption Kellgren[1] and Whitty and Willison[2] have shown that pain of a variety of types can be produced reflexly from the muscles (or, as Sinclair et al[3] prefer, the nerves within the muscles) of the back Is it not time that we investigate more carefully the part played by other parts of the invertebral joint in the production of symptoms such as acute lumbago?

Gloucester

J F BOURDILLON

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[1] Kellgren J H *Lancet*, 1949 i, 943
[2] Whitty, C W M, Willison, R G *ibid* Aug 2, 1958, p 226
[3] Sinclair, D C, Feindel W H, Weddell, G, Falconer, M A *J Bone Jt Surg* 1948, 30B, 515

HOOKWORM AND ANÆMIA

SIR,—We have read with great interest the recent correspondence on this subject

We do not suppose that there is any dispute that a sufficiently large hookworm load will cause anæmia

Dr Tasker's figures[1] suggest that a relatively moderate load of 800 worms may cause a daily loss of 80 ml of blood We have frequently counted 1000–3000 worms in the stools after giving a vermifuge Hookworm infection is so widespread in Africa that, although probably only a small proportion of those infected carry a sufficient load of worms to cause clinical anæmia, this small proportion is in absolute numbers so large as to constitute, in many places, a serious medical problem

We have recently carried out some observations which show that heavy, but not light, hookworm loads cause a demonstrable fall in the absorption of nitrogen from the intestine Ventkatachalam and Patwardhan[2] have shown that ascaris can behave similarly, and Stewart[3] showed that *Hæmonchus contortus* diminished nitrogen absorption in the sheep Various authors have claimed that ascaris secretes an antiproteolytic substance into the intestine, and Stewart has claimed that *H contortus* does this in the sheep So far as we are aware, the question of the production of an antiproteolytic substance by hookworms has not yet been investigated

Apart from any effect of parasites, there is evidence that a diet low in protein by itself decreases nitrogen absorption[4–6]

May not the sequence of events be somewhat as follows? In a population exposed to hookworm infection, those on a diet poor in protein secrete a diminished amount of proteolytic enzymes in the intestine Hookworms, on reaching the gut, thus find it relatively easy to establish themselves They produce their antiproteolytic substance, still further damaging the host's power of absorbing nitrogen, and therefore his power to secrete digestive enzymes, so setting up a vicious circle Presumably the diminution of proteolytic enzymes will encourage the lodgment of fresh worms Conceivably protein depletion may also hamper the host's resistance to invasion by the infective larvæ Removal of the worms with the administration of iron will cure the anæmia—until reinfection occurs

Such a hypothesis would help to explain the observation that in some communities the percentage of persons harbouring hookworms is very high, but heavy loads and gross anæmia are rarely seen, and that those with heavy worm loads and gross anæmia so often give a history of having lived on a diet greatly deficient in protein

East African Medical Survey and
Research Institute,
Mwanza, Tanganyika

E G HOLMES
S J DARKE

SIR,—We have estimated the blood and iron losses in the stools of anæmic and non-anæmic patients with heavy, light, and no hookworm infection This has been done over periods of 40 to 50 days before giving a vermifuge and for 10 to 30 days afterwards

The blood and iron content of the stools were estimated using ^{59}Fe ($FeCl_3$) and ^{51}Cr (Na_2CrO_4) by the recognised techniques modified to meet our special requirements 10–15µc of ^{59}Fe and 100 μc of ^{51}Cr were given intravenously either as ferrated plasma or chromated cells and thereafter the whole stool collected daily The radioactivity was measured on each stool separately using a ring of six 10-inch halogen-quenched Geiger-Muller tubes The stools were then dried and powdered and re-read in the counter, as well as in a plastic wrap-round pot in a scintillation counter, using a thallium-activated sodium-iodide crystal Plasma-volumes, red-cell mass, and iron clearances and utilisation were determined and the expected pattern for hypochromic anæmias found

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[1] Tasker, P W G *Lancet*, 1958, i, 1226
[2] Ventkatachalam, P S, Patwardhan, V N *Trans R Soc trop Med Hyg* 1953, 47, 169
[3] Stewart, J Report of Director of Institute of Animal Pathology, Cambridge, 1932–33, p 77
[4] Thompson, M D, Trowell, H C *Lancet*, 1952, i, 1031
[5] Platt, B S Report of Second Inter-African (C.C T A) Conference on Nutrition, Gambia, 1952, p 153 H.M Stationery Office, 1954
[6] Pellet, P L *Proc Nutr Soc.* 1957, 16, x.

The following data refer to an anæmic adult male African patient with many hookworm eggs in the stool who entered hospital on May 23, 1958 Hæmoglobin (Hb) 3 7 g per 100 ml, mean corpuscular Hb concentration 25%, packed-cell volume 14%, a very active erythronormoblastic sternal marrow Free HCl in gastric juice Given 1 0 g (gr 15) of ferrous sulphate daily from May 29 to July 30 Hookworms still present but Hb rose to 14 6 g per 100 ml on July 8 Blood and iron *losses during the 39 days before worming totalled 470 ml* and 171 mg respectively (mean daily loss 12 ml and 4 4 mg)

Daily losses of blood were extremely variable (1 6 ml – 25 0 ml) emphasising the desirability of daily measurements As was to be expected, the iron losses increased as the Hb level rose, so that a similar blood loss will result in a greater iron loss in less anæmic patients

On July 8 the patient was given a vermifuge of tetrachlorethylene followed 3 hours later by a magnesium-sulphate purge 1100 *Necator americana*, 2 *Tænia saginata*, and a few ascaris were recovered from the stools passed during the next 48 hours A second vermifuge was given on July 25, but no hookworms or other parasites were recovered

The blood and iron losses were similarly estimated for 13 days after the vermifuge, and gave a total blood-loss of 24 ml and an iron loss of 12 mg with mean daily values of 1 8 ml and 0 9 mg

Since there are considerable intestinal mucosal losses (30–80 g daily) some part of the fæcal iron may have come from this source, in patients with heavy worm loads mucosal desquamation rates may be higher than in non-infected patients

The amount of radioactivity found in the hookworms was *equivalent to approximately 0 002 ml* blood per worm (=0 005 mg Fe) We do not regard this figure as in any way significant, since it is not the amount of blood that the worms consume that is important but their migratory browsing habits which may leave bleeding points in the mucosa and the possibility that they may " pump " blood through them in the act of sucking

Taking into consideration the variations in the hæmoglobin level during the whole period of observation before de-worming, 9 0 mg of Fe were lost in the first 13 stools passed after the dose of ^{59}Fe with a mean hæmoglobin during this period of 4 g per 100 ml, in the following 13 stools taken during the period when the average hæmoglobin was 7 g per 100 ml 18 mg of iron were lost, in the next 13 stools taken during the period when the hæmoglobin was 12 g per 100 ml, 74 mg of Fe were lost, and in the final 11 stools collected when the hæmoglobin was 15 g per 100 ml, 70 mg were lost Thus during the 39 days prior to the removal of the 1100 hookworms, 171 mg of iron were lost—a daily average of 4 4 mg In spite of heavy hookworm loads only on two occasions did the daily loss of blood exceed 20 ml (25 ml and 23 ml) and this when the hæmoglobin level was 4 0 g per 100 ml, thus giving an iron loss on these two days of only 2 5 and 2 0 mg

In the 13 days following the removal of the worms the patient lost 24 ml of blood and 12 mg of Fe, taken at a 15 g per 100 ml hæmoglobin He was discharged from hospital on July 26 with a hæmoglobin of 15 0 g per 100 ml

From the above facts it seems that

(1) Normal *hæmoglobin levels can be attained in very* severe iron-deficient anæmia by giving oral iron therapy alone while leaving the worms in situ even in cases such as the above that *have heavy hookworm loads*

(2) There are wide daily variations in the amount of blood and iron lost

(3) Heavy hookworm loads do not always produce significant blood and iron losses, and that there is not always a correlation between worm loads and blood-loss This blood-loss can be diminished by either iron treatment or transfusions, while leaving the worms in situ, indicating that worms are not the only factor involved[1,2]

(4) Iron losses, although diminished, may continue after the removal of the worms, perhaps owing to the temporary persistence of bleeding points in the gut

(5) *Similar blood-losses give rise to higher iron losses* as the hæmoglobin of the patient rises, a point not always appreciated

(6) Some of the iron liberated from the blood in the gut may be reabsorbed, although hæmoglobin is not a good course of iron

(7) *Intestinal cellular desquamation* may be high in parasite-infected patients and may account for some of the iron lost

It should not be concluded from this example that all patients having hookworms are anæmic or that all patients with iron-deficient anæmias in the tropics have hookworm

Full details of this work will be published elsewhere with the findings in anæmia without hookworms and in non-anæmic patients with hookworms

HENRY FOY
ATHENA KONDI
W H AUSTIN

Wellcome Trust Research Laboratories and
Government Electrical Engineering
Department, Nairobi, Kenya

NEUROTROPIC VIRUS IN AFRICAN MONKEYS

SIR,—In view of the increasing use of African monkeys for tissue-culture purposes, we wish to record that a virus resembling the B virus of Sabin and Wright[3] has been isolated twice in these laboratories from central-nervous-system tissues of the African vervet monkey *Cercopithecus æthiops pygerythrus*

This virus produces nuclear inclusions and small syncytia in cultures of monkey-kidney epithelium The intradermal and subcutaneous inoculation of rabbits is followed by marked necrosis of the skin and, in some instances, by paralysis and death, and the virus has been recovered from the brains and spinal cords of rabbits showing paralysis Neutralisation tests with anti-B virus *sera indicate that there is a serological relationship between* B virus and the agent we have recovered, which we have designated SA8 in the series already described by us[4]

H MALHERBE
R HARWIN

Laboratories of the Poliomyelitis Research
Foundation, South African Institute for
Medical Research, Johannesburg

UNSATURATED FATS AND IMPORT RESTRICTIONS

SIR,—Dr Bourdillon (Aug 23) is incorrect in stating that patients in Britain are unable to purchase corn oil Maize oil (corn oil) *B P C* is freely available for purchase by patients at retail chemists in the United Kingdom A simple, palatable emulsion containing approximately 50% of maize oil *B P C* can also be obtained by those who dislike the taste of pure maize oil

Both preparations are being prescribed A number of long-term clinical studies are also being *carried* out at different centres in view of the observation that the ingestion of certain vegetable oils will result in the lowering of a raised serum-cholesterol Published work suggests that maize or corn oil, given in adequate quantity, is probably *the most active* of these vegetable oils in its cholesterol-lowering property

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1 Roche, M, et al *J clin Invest* 1957, 36, 1183
2 Roche, M, et al *Nature Lond* 1957 180, 1078
3 Sabin, A B Wright, A M *J exp Med* 1934, 59, 115
4 Malherbe, H, Harwin, R *Brit J exp Path* 1957, 38, 539

It is to be hoped that as a result of such careful clinical investigations the practical value of maize oil in the treatment and prophylaxis of atherosclerosis will be properly assessed

Medical Department,
Boots Pure Drug Co Ltd, Nottingham E V B MORTON

HOW TO BE HAPPY THOUGH RESIDENT

SIR,—I wish I had been able to read Mr Bryan Jennett's article, in your last issue, five years ago when I first qualified I am sure it will save all new housemen who read it from finding out many things the hard way when they start in hospital

Putting yourself in the other person's position, writing down things clearly in case-notes, and dealing with the proper people are but three pieces of advice which in retrospect are invaluable

Liverpool C R PORTEOUS

Public Health

Influenza this Winter

MEETING in Stockholm recently with Dr C H Andrewes as chairman, the World Health Organisation's expert committee on respiratory virus diseases said that the A/Asia/57 virus is likely to be the predominant type in influenza outbreaks during the next few years People infected during the pandemic of 1957 are likely to have at least a basic immunity

Large quantities of vaccine, providing 60–70% protection, are now available in several countries From a clinical standpoint, its use is especially important for expectant mothers and people suffering from cardiovascular or lung disease, or metabolic disorders To offer maximum protection, it should be given at least a fortnight before influenza is expected to become epidemic There can be no question of stopping an epidemic by vaccination what is aimed at is limitation of its effects by preventing high death-rates and excessive absenteeism, such as might disorganise public services

Vice-chairman of the committee is Prof V M Zhdanov, of Moscow, and, among other advances in vaccine research, work in the U S S.R with attenuated live virus vaccines was reviewed Unlike the formalin-inactivated influenza virus, the live vaccine is not administered by inoculation but sprayed into the nose and throat Because of its high virulence, it is not recommended for children under 7 years old

Mention was made of a method—promising but unproven—by which stocks of vaccine may be made to go further by mixing with an "adjuvant" The possibility of an animal reservoir of human influenza was also discussed Several studies of this, initiated by W H O, are in progress

Carbon Dioxide in Harvested Grain

The Ministry of Agriculture, Fisheries, and Food has pointed out that grain harvested wet may give off carbon dioxide This can happen in any place where grain is stored, and the gas, being heavier than air, will collect in the pits or ducts of a grain-handling plant When carbon dioxide is detected by the extinction of a lighted match or candle, the place must be thoroughly ventilated Anyone working in these places who feels faint or dizzy should get out at once

Preservation of Citrus Fruits

The Minister of Agriculture, Fisheries, and Food and the Minister of Health, acting jointly, have made the Public Health (Preservatives, &c, in Food) (Amendment) Regulations, 1958, which permit the importation and sale of citrus fruit containing diphenyl or ortho-phenylphenol or admixtures of the two substances within prescribed limits

Obituary

CHARLES CADY UNGLEY

M.D Durh, F R C.P

Dr Ungley, who died at the age of 55 in the Royal Victoria Infirmary, Newcastle upon Tyne, on Aug 21, was a general physician, skilled especially in hæmatology and neurology, who in the midst of general hospital duties, teaching, and (for many years) private practice maintained a passionate interest and immense industry in research

He qualified in Newcastle in 1925, and, after a trip to the Far East as a ship's surgeon, he held resident appointments at the Royal Victoria Infirmary, taking his M D in 1927 and his M R C P in 1928 His research ability was soon apparent, and in 1930, with a Rockefeller studentship, he visited America, working at Harvard University and at the Massachusetts General Hospital He was appointed to the staff of the Royal Victoria Infirmary in 1933 and in 1935 was awarded a Leverhulme scholarship of the Royal College of Physicians to study pernicious anæmia In 1937 he was elected F R C.P, and in the following year he gave the Goulstonian lectures, on deficiencies of nutrition and their relation to disease

His chief interest was in pernicious anæmia and he developed fundamental techniques for the clinical assay of liver fractions As a by-product of this work he provided the Royal Victoria Infirmary with a first-class hæmatology service During the late war he served with the Navy, and his work on survival at sea was, and remains, of the highest importance It was based on immense labour in the collection of data, and included his special study of immersion foot But after the war he returned to pernicious anæmia and was at hand with a fully developed organisation for the first clinical trials of vitamin B_{12} His work on the comparison of vitamin B_{12} and liver extract in the treatment of subacute degeneration was an outstanding example of the careful elicitation of neurological signs and their expression in quantitative terms At the end of his life he was trying to extend this work using serial psychometric tests to study vitamin-B_{12} deficiency in the brain Of his continuous interest in this research F J N writes

"Charles Ungley was at once fascinated by the report by Minot and Murphy of the efficacy of liver diet in the treatment of pernicious anæmia and was one of the first to demonstrate the remarkable improvement which could often be obtained by early treatment of subacute combined degeneration of the cord with liver One of his earliest papers, published in the *Newcastle Medical Journal* in 1929, was on this subject He continued with this work after the war and the results of his most meticulous studies were published in *Brain* in 1949 The great developments of hæmatology opened up by the discovery of the liver treatment found him in the forefront of clinical and experimental research Under the stimulus of Castle's hypothesis he strove to determine the nature of the extrinsic and intrinsic factors, and, most notably, collaborated with Lester Smith in testing the potency of purified liver extracts and ultimately of vitamin B_{12}"

Ungley was deeply conscious of his responsibilities to his students His firms were always happy ones He enjoyed teaching and was good at it, and those who came to his ward, especially on a Saturday morning, were well rewarded. Himself a specialist of specialists, he was determined that his ward clerks should see medicine in a wider setting, and, long before it became official policy to do so, he used to arrange for them to visit a number of general practitioners during their appointment. Of this scheme A. S. relates:

"Ungley approached four general practitioners (of whom I was one), with urban, semi-urban, rural, and small-town practices, and persuaded each to take a student for one day weekly and show him something of general practice. This scheme differed from most others which have been introduced since, in that the student saw different types of practice and different doctors, and saw them at the beginning of his hospital career. This made him realise that patients are people with homes and families, not merely vehicles of disease, and coloured his later dealings with patients in hospital."

The affection, as well as respect, which Ungley inspired is shown by R. E. I.'s words about his old chief:

"Charlie's figure was slight and athletic, his manner diffident, and he always looked a little windswept (he loved to drive an open car). Any conversation was punctuated by the frequent lifting of his eyebrow to a fascinating height. His later years were dogged by illness, but he never allowed this to diminish his appetite for life. A few years ago he took up gliding, and his pleasure was infectious when he passed the tests that entitled him to fly solo. When ill health put an end to flying he took up art, and in the last year of his life achieved some notable oils. Despite his world-wide reputation he remained the most modest, lovable, and approachable of men, and he always retained something of the simplicity of childhood. He was sometimes shy with adults but he was always at home with children and they loved him. No-one who saw him dancing with a little girl who came downstairs in her nightgown in the middle of a party, or who watched him cooking sausages at a family picnic, could doubt that, stricken though he was in health, he would never lose the secret of youth. To work with him was to receive a priceless education in clinical investigation; it was also to have contact with a human spirit of the rarest quality."

Dr. Ungley leaves a widow, a son, and two daughters.

HUGH ARTHUR SANDIFORD

M.C., M.B. Manc., D.P.H.

As the first director of Army psychiatry and again as the first director of the Commonwealth and the International Advisory Bureaus of the British Medical Association, Brigadier Sandiford proved his worth as a pioneer medical administrator.

He was born at Manchester in 1892 and educated at the grammar school and university of that city, qualifying in 1914. Almost at once he joined the R.A.M.C., and in 1917 he was awarded the M.C. for gallantry while looking after casualties under heavy artillery fire. After the war he decided to remain with the R.A.M.C., and in the next years he gained valuable experience both of clinical medicine and of administration. In 1925 he took the D.P.H. and in 1933 he was appointed instructor at the Army School of Hygiene. Later he became assistant director of hygiene at the War Office and deputy director of hygiene in Eastern Command.

At the beginning of the late war his wide experience of physical assessment persuaded him of the importance of devising suitable methods of selection, and his interest in this task led in due course to his appointment as director of Army psychiatry at the War Office. His success in what was not an easy assignment was appreciated by his psychiatric colleagues, one of whom, T. F. R., writes:

"It is no secret that the rise of psychiatry during the early years of the war was viewed with disquiet by many senior members of the Army Medical Services. When it became necessary nevertheless to provide adequate administrative arrangements for these developments, it was a relief to many to know that a Regular as wise and as moderate as Sandiford had been appointed director of Army psychiatry. To our surprise we psychiatrists quickly learned that we had acquired a good friend whose understanding and confidence in the potential value of the contribution we could make to preventive medicine was greater than our own. He may have exerted a steadying influence upon us, but—what was far more important—he inspired us to work in new directions. His own World War I experience led him to take a special interest in the problems of repatriated prisoners of war and, as a result, psychological studies were made which resulted in the setting up of civil resettlement units towards the end of the war. The experience thus gained has led to many other experiments in rehabilitation of a similar kind and to the setting up of other therapeutic communities, but the first insight which led to these experiments in social psychiatry we owe to Sandy. He was a quiet man whose sincerity and integrity showed itself in all his actions, and he very easily won the trust and affection of all who worked with him."

During his years in the Army he had met and worked with medical officers from many parts of the world, and especially of course from the British Commonwealth. When, in 1947, shortly after he retired from the Army, the B.M.A. decided to set up their advisory bureaus to help medical visitors from abroad, Sandiford was chosen, from over a hundred applicants, as director of the new venture. His talents for kindliness and organisation complemented each other, and he offered those who came to the bureaus a friendly welcome backed by useful information and practical advice. Of this second stage of his career a colleague writes:

"Sandiford was well suited for his work at the B.M.A. He was shrewd and often blunt, but he was above all a kindly man, interested in human affairs. His work bore the mark of the skilled administrator, but, unlike many administrators, he was capable of the liveliest initiative when need arose. The need did arise when Hungarian doctors began to arrive in this country as refugees in the autumn of 1956. Of the two score or so who reached here, nearly all soon found their way to Sandiford's office. No matter what their needs—a passage to South America, thirty shillings for a train fare, accommodation in Scarborough, a new suit, news of relatives in Budapest, a job in Bristol—Sandiford did his best, and, because (despite his genial air) he did not shrink from ruthless unorthodoxy, he usually succeeded. The ripples of the Hungarian revolution have died away, but it is certain that the doctors who then came to England will not forget Sandiford—equable, courteous, benign, and wise, always ready to listen and to act."

Brigadier Sandiford retired from his work with the B.M.A. last year and he died on Aug. 13 at his house in Windsor. He leaves a widow, two daughters, and a son, Dr. R. H. Sandiford.

Dr. J. BROCK BISHOP

P. G. McG. writes:

"Brock Bishop had a tremendous zest for the full life. His interests were wide, and to each one of them—social, professional, and purely recreational—he gave a full measure of his abundant energy. I saw this mainly in his medical work, where his conscientious attention to every facet of the life of his patients not only paid handsome clinical dividends, but earned him the respect and deep affection of patients and colleagues. His devotion to duty did not result in a dreary rigidity, but was clothed in a vivid, flexible human approach, the patients' own attitude and susceptibilities would extract from Brock the formal courtesy of which he was a master, or through the whole gamut to a friendly raciness of language which on occasion enlivened his reports as well. The memorial which he would appreciate most is the affectionate smile which comes to every face in Broadmoor at mention of his name."

CHEVALIER JACKSON

M.D. Jefferson, D.Sc. Penn., LL.D. Temple

Chevalier Jackson was born in Pittsburgh in the last year of the American Civil War. As a frail sensitive child he was shocked by the brutal sports and cruelty of the farming and coalmining community in which he grew up, and at school he was exposed to merciless bullying. The misery of these years was mitigated by the happiness of his home where he was encouraged to read, to draw, and above all to make things.

He began to use wood and sharp tools at the age of four and thereafter, he wrote, "I was never without a workshop; later it was called a laboratory, but it was always a place for constructive work." Carpentry was his first manual skill. In the next difficult years he acquired others, and his thrifty genius wasted none. At the family hotel he was put in charge of the uncertain gas-generating plant and water system. To fit himself for this task he served a summer vacation as a plumber's apprentice. His experience with tubes and valves led later to his discovery that in the heart and lungs there are mechanisms parallel to the stop valves, by-pass valves, and check valves of pipes, pumps, and plumbing. "My whole life's work with the air and food passages seems curiously parallel in its fundamentals to those boyhood days as a plumber's cub." To earn money to pay for his first year at college he worked as a china and glass decorator, painting apple blossom and butterflies on lamp shades and stands. Later this talent allowed him to reproduce what he saw for medical illustrations in colour.

His medical training was only accomplished with difficulty. After a year with a "preceptor", Dr. Gilmore Foster, he entered Jefferson College, Philadelphia, in 1884. When his fees had been paid, he was left with 63 cents a day for all his other expenses. In the long vacation he sold medical books on commission, and sailed as ship's cook to the cod-fishing in Newfoundland. The M.D. course in those days was two years, and he graduated in 1886 still six months short of the legal age of twenty-one.

The new graduate had already chosen his specialty. A dispensary for diseases of the ear, nose, and throat had lately been set up in Philadelphia, and as a student he had attended it regularly. His teacher, Dr. J. Solis Cohen, had lent him a complete set of the writings of Morell Mackenzie, and he decided without delay to visit Mackenzie's clinic in London. He accumulated a little money and sailed steerage for Europe and London. He stayed as long as his funds held out, and on his return to Philadelphia boldly set up in consultant practice.

To begin with much of his practice was among the children of the poor. The value of tonsillectomy was becoming more widely recognised, and Chevalier Jackson was so convinced of its merit that he offered to examine and operate on the children in the local schools. In those days, too, stricture of the larynx was often the tragic sequel to diphtheria, and he won a reputation for his skill in treating these children by tracheotomy and by intubation. In nearly every American kitchen lye was used as a cleaning material. It looked like sugar and too often it stood unlabelled, tempting and unguarded. If a child put it in his mouth, the oesophagus was burnt and the contracting scars gradually closed the passage till the child died of starvation. The misery of these small patients led Chevalier Jackson to embark on his long campaign (which only succeeded in 1927) to make it compulsory that preparations containing this dangerous substance should carry a poison label and a warning to keep them out of the reach of children.

In treating these small patients he used an instrument which he had adapted from a device he had first seen in Morell Mackenzie's clinic. In his hands the instrument was improved, a light carrier was added, and it became the oesophagoscope. As well as for lye strictures he used it for the removal of foreign bodies. For his diphtheria patients he was already using a laryngoscope, and his skill and success with these instruments led him to the study of bronchoscopy. His belief in the value of these new techniques forced him into the role of teacher and soon he was giving bronchoscopic courses in Pittsburgh, Philadelphia, and Paris.

In 1911 his work was restricted, though not interrupted, by his first attack of tuberculosis. He was ordered to supplement his austere diet and to spend 12 out of every 24 hours in bed. Though much of his bed rest was spent in annotating his case-records and making sketches of laryngeal and endoscopic views of pathological tissue, his infection was halted and in six months he was back at work. But two years later he had a recurrence, and renewed bed rest was ordered. With some misgivings, for the sake of his health he gave up the most remunerative part of his practice—tonsil and adenoid operations—and henceforth limited his specialty to laryngoscopy, bronchoscopy, oesophagoscopy, and gastroscopy. He also used his enforced rest to write his book on *Peroral Endoscopy and Laryngeal Surgery*, which was published in 1915.

As early as 1900 he had been elected to the chair of laryngology in the Western Pennsylvania Medical College, later the University of Pittsburgh, and with the years his reputation grew steadily. In 1915 the New York Post-graduate Medical School appointed him professor of bronchoscopy and entrusted him with the organization of a new department of bronchoscopy, but he had only held this chair a short time when his third attack of tuberculosis forced him to resign. Despite his uncertain health, in 1916 he made the decision to "pull up stakes" and move from Pittsburgh to Philadelphia, where he had been offered the chair of laryngology at Jefferson College. Academic posts then offered prestige and opportunity but no salary, and the move meant giving up a private practice which was just beginning to be lucrative to start again from the beginning. But his welcome from his colleagues in Philadelphia heartened him, and three years later the University of Pennsylvania created for him a chair of bronchoscopy and oesophagoscopy, and in 1924 Jefferson College followed their example. To this formidable array of chairs, almost all specially endowed for him, he later added chairs at Temple University and at the Women's Medical College of Pennsylvania (of which he was also president).

He accepted his responsibility as one of the founders of a new specialty and travelled all over the world to give lectures, attend conferences, and share in discussions.

Many of his colleagues in this country will still recall his address to the British Medical Association at Bath in 1925. One of them later wrote[1]: "The slight puckish figure, clothes loosely fitting and collar two sizes too large . . . with a rubber manikin and gleaming instruments, drawing chalk diagrams with both hands, showing more and more lantern slides and short cinema films, and talking and talking with enthusiasm, straight on for two hours " On many of his journeys he received professional, academic, and national honours His appointment as officer of the Legion of Honour of France was particularly appropriate, for he was linked to that country by ties of kinship

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[1] Scott Stevenson, R. In a Harley Street Mirror, p 140 London, 1951

In his private life, too, Chevalier Jackson was always aware of his specialty His simple and austere life may not have been uncongenial, but abstinence from tobacco and alcohol, his abstemious, vegetarian meals, his habit of wearing gloves, all safeguarded the dexterity of his sensitive fingers and the steadiness of his eyes and nerves

Soon after he came to Philadelphia he and his wife settled in an old grist and saw mill about 35 miles from the city With characteristic ingenuity the grist mill was repaired and induced once more to earn its keep and to provide the house with electricity In this family retreat Chevalier Jackson was able politely to evade unwelcome social engagements (and nearly all social engagements were unwelcome) and to spend his time in his workshop, writing in a boat on the mill stream, and reading or painting at his study window where he shared the sill with rabbits, quails, and birds

He died on Aug 16 in the hospital of Temple University, Philadelphia, where his son, Dr Chevalier L Jackson, is now professor of laryngology and broncho-œsophagology

One of his British colleagues, V N , writes

" The death of Chevalier Jackson marks the end of an epoch in advancement of the knowledge and treatment of diseases of the lungs and œsophagus He added very greatly to methods which not only allowed of instrumentation within the air and food passages but also carried forward investigations into the physiology and pathology of these regions His early days were ones of struggle and of financial difficulty, with tenacity of purpose he concentrated his energies on endoscopic methods in the trachea, bronchi, and œsophagus, though he had difficulty in convincing the medical profession of the importance of this approach

" Of the many distinctions, both in America and in other parts of the world, which came to him, the most important included his election as honorary fellow of the Royal Society of Medicine of London, of the Scottish Society of Otology and Laryngology, and of the Royal College of Surgeons of Edinburgh, and as laureat of the Académie de Medecine of Paris Perhaps one of his most illuminating honours was the conferring on him in 1952 of the Medallion of the American College of Chest Physicians, which emphasises the recognition by the medical profession of his extremely valuable contributions to the field of the chest physician and thoracic surgeon His memory will be treasured by innumerable friends and students who for long have recognised the value of his pioneer work "

Our photograph is of a bust by Luigi Maraffi, presented to Chevalier Jackson by a group of his pupils and colleagues in 1937

Appointments

BRADSHAW, D B , M B Dubl , D P H M O H and principal school M O , Leeds

CAMPBELL, R J C , M B Edin , D M R consultant radiologist, Stracathro Hospital, Brechin, Brechin Infirmary, Arbroath Infirmary, and other Angus area hospitals

CECIL, J T , M B Lond D P H assistant M O , Maidstone area, Kent

GRIFFITH EIRWEN, M B Lond assistant M O , Medway towns area, Kent

MANGAN, GEORGE, M R C S D O ophthalmologist, Ongar, Epping, and Waltham Abbey refraction clinics

MORRIS, P A L A H Dubl , D P M senior assistant psychiatrist, Kingsway Hospital, Derby

SMITH, D ROBERTSON, M D Cantab consultant pathologist, Reading area pathology service

SUMMERS, HARRY, M B Manc , M SC Brist assistant M O , Mid-Cheshire area

Notes and News

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued th following new supplementary list of approved names

Approved Name	*Other Names*
Ambazone	1 4-Benzoquinone amidinohydrazine thio semicarbazone hydrate Iversal
Beclamide	*N*-Benzyl-β-chloropropionamide Nydrane
Benztropine	3-Diphenylmethoxytropane Cogentin is the methanesulphonate
Bisacodyl	Di-(*p*-acetoxyphenyl)-2-pyridylmethane Dulcolax
Chlorphenesin	3*p*-Chlorophenoxypropane-1 2 diol
Clemizole	1-*p*-Chlorobenzyl-2-pyrrolidinomethyl-benzimidazole Allercur is the hydrochloride
Clemizole Penicillin	Benzylpenicillin combined with 1-*p*-chlorobenzyl-2-pyrrolidinomethyl-benzimidazole Megacillin, Neopenyl
Deanol	2-Dimethylaminoethanol *Atrol is the bitartrate*
Dimethisterone	6α 21-Dimethylethisterone Secrosteron
Ethoheptazine	Ethyl (±)-1-methyl-4-phenylazacycloheptane-4-carboxylate Zactane
Framycetin	An antibiotic derived from *Streptomyces decaris* Soframycin is the sulphate
Furazolidone	3-(5-Nitrofurfurylideneamino)oxazolidin 2 one Furoxone
Inproquone	2 5-Bisethyleneimino-3 6-dipropoxy-1 4-benzoquinone
Pempidine	1 2 2 6 6-Pentamethylpiperidine Perolysen is the hydrogen tartrate, Tenormal is the hydrogen tartrate
Phytomenadione	2-Methyl-3-phytyl-1 4-naphthaquinone Vitamin K_1 Konakion, Mephyton
Piprinhydrinate	Diphenylpyraline salt of 8-chlorotheophylline 4-Diphenylmethoxyl-1-methyl-piperidine salt of 8-chlorotheophylline Kolton, Mepedyl
Sulphaethidole	5-*p*-Aminobenzenesulphonamido 2-ethyl-1 3 4-thiadiazole *Sethadil*
Sulphathiourea	*p*-Aminobenzenesulphonylthiourea Badional
Trimethidinium	(+)-3-(3-Dimethylaminopropyl)-1 8 8-trimethyl-3-*azabicyclo* [3 2 1] octane di (methyl methosulphate) Camphidonium

INDEX

Proprietary Name	*Approved Name*
Allercur	Clemizole
Atrol	Deanol
Badional	Sulphathiourea
Camphidonium	Trimethidinium
Cogentin	Benztropine
Dulcolax	Bisacodyl
Furoxone	Furazolidone
Iversal	Ambazone
Kolton	Piprinhydrinate
Konakion	Phytomenadione
Megacillin	Clemizole Penicillin
Mepedyl	Piprinhydrinate
Mephyton	Phytomenadione
Neopenyl	*Clemizole Penicillin*
Nydrane	Beclamide
Perolysen	Pempidine
Secrosteron	Dimethisterone
Sethadil	Sulphaethidole
Soframycin	Framycetin
Tenormal	Pempidine
Vitamin K_1	Phytomenadione
Zactane	Ethoheptazine

INFANTILE DIARRHŒA AND VOMITING IN IRELAND

In the Medical Research Council of Ireland's report for 1957,[1] Dr Owen Conor Ward and Dr Desmond Donovan describe a survey of the incidence and epidemiology of infection by the *Escherichia coli* strains which have been held responsible for communicable diarrhœa and vomiting in infants

The investigation was started on the opening day of a new hospital—Our Lady's Hospital for Sick Children—at Crumlin. For nearly a year rectal swabs were taken on admission and then weekly from infants under the age of two—numbering 647 in all These children were not drawn from one area although most came from Dublin city, many were from country districts

On admission, the rectal swabs of 69 patients were positive for the *Esch coli* variants, of these 62 had diarrhœa or vomiting, or both 329 patients had diarrhœa or vomiting but negative rectal swabs, and in 118 of these no satisfactory explanation of the symptoms was found In general, these were not so ill as the children from whom escherichia strains were recovered only 22 of the 329 were severely dehydrated (and 6 of these had been in contact with pathogenic *Esch coli*) whereas 12 of the 69 swab-positive cases showed such dehydration

All the infants were nursed in separate cubicles by trained staff, yet there was cross-infection with *Esch coli* in at least 31 cases Dr Ward and Dr Donovan conclude, therefore, that dissemination of the infection cannot be prevented by ordinary nursing techniques

MEDICAL SERVICES OF PAPUA AND NEW GUINEA

In our advertisement columns this week the Territory of Papua and New Guinea is advertising the post of assistant director of medical research As local conditions of life and medical practice will be unfamiliar to many of our readers, the Director of Public Health has sent us some notes about them

The combined territories, he points out, include half the mainland of New Guinea and all the islands to the north and north-east Their area is 183,600 square miles and the population 1¾ million, of whom 18,000 are not Papuans Communications by road are limited by mountains and fast-flowing rivers, but air services connect most districts

The people live in villages and hamlets and depend on a subsistence economy, but primary and secondary industries are gradually raising the standard of living The two most important diseases are malaria and tuberculosis Others are filariasis, helminthiasis, amœbic and bacillary dysentery, leprosy, yaws, and venereal diseases, to which may be added such general medical problems as anæmia and pneumonia, with cirrhosis of the liver and kwashiorkor in certain areas

The department of public health, with headquarters at the capital, Port Moresby, provides the curative and preventive services offered by local and central government health authorities in other countries Its doctors also undertake some private practice, and there are other private practitioners in the main centres of Port Moresby, Lae, and Rabaul The department is administered by a director, with assistant directors responsible for divisions of medical services, preventive medicine, medical training, infant child and maternal health, and administration There is a European staff of 80 doctors, 146 medical assistants, 138 trained nurses, and 172 ancillary and clerical staff The indigenous staff consists of 4500 Papuans and New Guineans most of them are semi-skilled orderlies, with a gradually increasing educational level The Christian missions also have a medical staff of 137, of whom 12 are doctors There are 98 hospitals scattered over the entire territory, and 1200 aid posts or dispensaries in the villages

Port Moresby General Hospital, the base hospital for the entire territory, is to be the centre for future medical research It has 370 beds The buildings are of a modern design including air-conditioned laboratories, theatres, and X-ray department The medical staff consists of a medical superintendent, surgeon, anæsthetist, physician, ophthalmologist, pædiatrician, two radiologists, pathologist, chest physician, and 4 resident medical officers The hospital is also a training centre Nurses' training has begun and a medical school is to be opened in 1960 for assistant medical practitioners, along the same lines as the Central Medical School at Suva, Fiji

The aim of the department is to improve the standard of public health in the villages and hamlets, and the emphasis is accordingly being shifted to preventive as opposed to curative medicine But preventive medicine needs basic research into the problems to be controlled, and it is with this need in view that it has been decided to add to the department a division of medical research

In the past, research has been undertaken by isolated individuals, in addition to their normal duties Studies in progress at present include an investigation into kuru, an obscure nervous condition that is almost 100% fatal and probably of hereditary origin Infant and child mortality is also of great local concern.

MEDICAL CERTIFICATES FOR LONG ILLNESSES

The Ministry of Pensions and National Insurance wishes to remind doctors that the Medical Certification Rules allow them, where a patient has been unfit for work for at least 6 months and incapacity is likely to last for some time to come, to give him a single certificate to cover up to 13 weeks ahead even though it may be necessary to see him more often

This arrangement was originally made so as to reduce the amount of routine certification by doctors, and the number of times the patient has to send documents to the local offices of the Ministry It also reduces the routine work in the local offices which has to be done on each claim for benefit When long-term certificates are issued, local offices are able to pay sickness benefit by means of order books covering 8 or 13 weeks, instead of preparing and sending postal drafts week by week. In the last few years the number of prospective certificates issued by doctors has decreased steadily and this has added disproportionately to the work in local offices

Local offices are writing to doctors where they know of cases in which it appears that long-term certificates might be appropriate But it is, of course, entirely at the discretion of the doctor whether he issues long-term certificates or not, and doctors are assured that the Ministry's action is not in any way an attempt to interfere with their discretion

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University of London

Dr R C Curran, senior lecturer in pathology in the University of Sheffield, has been appointed to the chair of pathology at St Thomas's Hospital Medical School

Dr Curran graduated M B with commendation from the University of Glasgow in 1943 He served with the R A M C and held house-posts at Glasgow Royal Infirmary before he was appointed assistant pathologist and bacteriologist to Stobhill Hospital Before taking up his present post, he was lecturer in pathology in the University of Glasgow In 1956 he was awarded the Bellahouston medal for his M D thesis His published work includes papers on collagen formation in the quartz focus, elaboration of mucopolysaccharides by vascular endothelium, and utilisation of sulphate ion by fibroblasts in quartz focus

Dr M de Burgh Daly, Locke research fellow of the Royal Society in the department of physiology at University College, has been appointed to the chair of physiology at St Bartholomew's Hospital Medical College

Dr de Burgh Daly studied medicine at the University of Cambridge, where he took the natural sciences tripos in 1944, and at St Bartholomew's Hospital After qualifying in 1947, he held a house-appointment at Barts and later became a lecturer in physiology at University College, London In 1952 he was awarded a Rockefeller travelling fellowship and the following year the Schafer prize in physiology He has contributed to Winton and Bayliss's *Human Physiology* and has published papers on innervation of the bronchi and on bronchomotor and pulmonary arterial reflexes

Society of Apothecaries of London

Dr W S C Copeman has been elected master, with Dr R R Trail and Dr Charles White as wardens

The following diplomas have been granted

M.M S A—P R Sathyanadhan

L M S S A—D H Perkins, J R. Carling, M C Liu, I H Bales, R J Priddy, J R Johnson R N Brain, S K C R. Villayarayan, M A Saber, E M Blenkinsopp, P W F Chan, N Mustapha, J A Saunders, D F Fergie-Woods, M T Haslam, H Hunt, E McIlwaine, P Nour-Eldin, J F Rivers M Budd, L B Cannell, A J Casson, M A Gibson, A M Hazell, R G Hornung, J G Williams

D.I.H—F de S Donnan, G F Smith W O Thompson.

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[1] The Council's office is at 50, Merrion Square, Dublin.

University of Otago

Next February, at the age of 70, Sir Charles Hercus will be giving up his post as dean of the Otago *Medical School* He is to continue part-time work as medical secretary to the New Zealand Medical Research Council Dr Edward G Sayers, C M G, consulting physician in Auckland, has been appointed to succeed him

Dr Sayers qualified in Otago, and after postgraduate study in London worked as a medical missionary in the Solomon Islands He returned to Auckland to practise as a physician before the war, in which active service took him to various theatres, and he attained the rank of colonel He has recently retired from the presidency of the Royal Australasian College of Physicians, and he is a fellow of the London college and an honorary fellow of the American one He is chairman of the New Zealand Medical Council and serves on a number of committees in the Health Department dealing with specialist services Last year he visited Canada, the U S A, and Great Britain

College of General Practitioners

Dr E F Scowen will give the Pfizer lecture at 9 P M on Wednesday, Oct 15, at St Bartholomew's Hospital *Medical* College, London, E C 1 His subject will be Some Difficulties in Prescribing

British Congress of Obstetrics and Gynæcology

This congress will be held in Cardiff from July 14 to 16 under the presidency of Prof Gilbert Strachan The programme is to be published in November The congress secretaries may be addressed at the *Maternity Hospital*, Glossop Terrace, Cardiff

Nutrition and Teeth

The Nutrition Society will hold a symposium on this subject at the London Hospital Medical College, E 1, on Saturday, Oct 4 Further particulars may be had from Miss D F Hollingsworth, c/o Ministry of Agriculture, Fisheries and *Food, Great Westminster House, Horseferry Road*, S W 1

Space Medicine

The British Interplanetary Society, with the cooperation of the Royal Air Force Institute of Aviation Medicine, is to hold a symposium on this subject at B M A House, Tavistock Square, London, W C 1, on Oct 16 and 17 Further particulars may be had from the secretary of the society, 12, Bessborough Gardens, S W 1

Imperial Cancer Research Fund

The Fund has announced the following staff changes

Dr J Craigie has resigned his post as director of the Fund's Mill Hill laboratories so that he can devote himself entirely to research in the laboratories His advice on problems of research will thus continue to be available to the Fund

Dr R J C Harris is joining the scientific staff on Oct 1, 1958, to take up a new appointment as head of the division of experimental biology and virology *He will also be responsible* (under the director, Dr G F Marrian) for the general administration of the Mill Hill laboratories

Dr A R Currie, at present assistant pathologist at the Royal Infirmary, *Glasgow*, has been appointed head of the division of pathology, and will take up *his duties on* Oct 1, 1959 The Fund is meanwhile giving financial support to the cancer research he is doing in the pathology department of the University of Glasgow

International Federation of Medical Electronics

At a meeting held in Paris in June, at the invitation of Dr Vladimir K Zworykin, of the Medical Electronics Center of the Rockefeller Institute, with the cooperation of UNESCO and a number of scientific societies, 76 representatives from eleven countries unanimously agreed

To set up an international federation of medical electronic organisations open to societies and individuals from all countries of the world, to hold an international meeting in Paris in the spring of 1959, to compile an international bibliography on medical electronics

Interim officers elected by the group include Dr V K Zworykin, president, Dr C N Smyth, vice-president and chairman of publications committee, and Mr B Shackel, treasurer

Royal Institute of Public Health and Hygiene

On Monday, Oct 13, at 5 P M, at the Institute, 28, Portland *Place*, London, W 1, Dr B G B Lucas will give the Bengue lecture His subject is to be artificial aids in the control of the circulation

Charterhouse Rheumatism Clinic

On Friday, Oct 10, at 5 30 P M, at 54, Weymouth Street, London, W 1, Prof *S* de Sèze, of the Centre de Rhumatologie Viggo-Petersen, Paris, will give the Gilbert Scott lecture He is to speak on postmenopausal trophostatic *pain*

Scientific Film Association

A medical section of this association is being formed and the inaugural meeting will be held on Monday, Sept 8, at 6 P M *at the film theatre*, room 103, Shell-Mex House, Strand, London, W C 2, when *Stress and the Adaptation Syndrome* (U S A 1957) and *Jugular Venous Pulse* (Great Britain, 1958) will be shown Further information may be had from the secretary at the association's new address, 3, Belgrave Square, London, S W 1

On Thursday, Oct 2, at 3 P M, at the Royal College of Physicians of London, Pall Mall East, S W 1, Sir Hartley Shawcross will give the inaugural address to Charing Cross Hospital Medical School

The National Association for the Prevention of Tuberculosis and Diseases of the Chest and Heart, with the chest clinic service of Glasgow, is holding a symposium on the catarrhal child, on Wednesday, Oct 1, at 3 30 P M, at the Royal Faculty of Physicians and Surgeons, 242, St Vincent Street, Glasgow, C 2 Prof Stanley Graham will be in the chair and the speakers will include Dr Catriona Sinclair, Dr A W Lees, Prof J W Howie, Dr William Blair, Dr R H Dobbs, Prof Wilfrid Gaisford, and Dr R J Cuthbert Tickets (10*s*) may be had from the N A P T Scottish Branch, 65, Castle Street, Edinburgh, 2

The *British* Commonwealth and Empire Nurses War Memorial Fund has awarded twelve scholarships for 1958–59 Nine go to nurses and midwives in the United Kingdom and three to nurses from the Commonwealth

The Scottish group of the Nutrition Society is holding a symposium in Edinburgh on Saturday, Sept 27, on nutritional hazards caused by radioactive contamination of foods Further particulars may be had from Dr J Davidson, Rowett Research Institute, Bucksburn, *Aberdeenshire*

Dr J W Galloway is to *succeed* Dr T H J Douglas as chief dental officer of the Department of Health for Scotland at the end of the year

Dr J *M* Walshe is spending two months in Argentina and Chile under the auspices of the British Council He is to visit the Universities of Buenos Aires, Cordoba, Rosario, and Chile

The Danish Surgical Society has become a member institution of the International Federation of Surgical Colleges

The second Doctors' Hobbies Exhibition *is to* be held at B M A House, Tavistock Square, London, W C 1, from Nov 10 to 14 Entry forms may be had from the public relations officer, Benger Laboratories Ltd, Holmes Chapel, Cheshire Entries close on Sept 12

The editorial and publishing offices of the *Pharmaceutical Journal* have been moved to 17, Bloomsbury Square, London, W C 1

A second edition of Notes on the Diagnosis of *Occupational* Diseases prescribed under the National Insurance (*Industrial* Injuries) Act has been published by H M Stationery Office (3*s*) The *notes* were compiled in 1950 *for the* guidance of doctors examining, for the Ministry of Pensions and National Insurance, claimants to benefit Since then three new diseases (tuberculosis, primary neoplasm of the epithelial lining of the urinary *bladder, renal pelvis,* or *ureter, and* cadmium poisoning) have been added to the schedule of prescribed diseases, and the schedule has been revised and reorganised on the lines of the recommendations made by the Industrial *Injuries* Advisory Council

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CORRIGENDUM *Eponyms in Medicine* —In this annotation (Aug 30, p 452) we described Thomsen's disease as amyotonia congenita, whereas it is really myotonia congenita—a much *different* disorder Our error illustrates with disconcerting immediacy the need *for the* advice, which we offered in the same annotation, that when eponyms are used "contributors and editors must strive to ensure that they are placed in a correct context and accurately rendered"

The Lancet · Saturday 13 September 1958

MALIGNANT DISEASE OF THE URINARY TRACT *

Sir Eric Riches
M C, M S Lond., F R C S
SURGEON AND UROLOGIST, THE MIDDLESEX HOSPITAL, LONDON, W 1

1773, the year of the foundation of the Medical Society of London by Lettsom and of the Boston Tea-party, also saw the birth in Frankfurt of a certain Bozzini He was the inventor of the first cystoscope, a primitive instrument in which light from a candle was reflected down a long tube passed into the bladder Two years after the delivery of the first Lettsomian lecture Desormeaux added a lens and a gas lamp, and in 1876 Nitze produced the prototype of the modern cystoscope The discovery of X rays by Rontgen in 1895 was another milestone in urological diagnosis, and it was in the same year that Rehn reported an increased incidence of bladder tumours among aniline dye workers

THE BLADDER

I have reviewed the notes of 565 of my patients with carcinoma of the bladder No cases have been included unless malignancy was verified either histologically at the time or by subsequent events The sex-incidence was 417 males to 148 females Their ages ranged from twenty-three to ninety, with an average of sixty-two years

Pathology

Types

Carcinoma of the bladder is seen in two main forms which differ so much in appearance and behaviour as to suggest two different diseases

On the one hand there is the *papillary tumour* it resembles the benign papilloma, save that its villi tend to be more stunted, its pedicle is wider, and its surface is often flecked with phosphates These tumours may be single, but they are often multiple or confluent, they should be regarded as a disease affecting the mucosa of the whole bladder They can spread in a wound by spill and implantation when the bladder is opened, and such implants often lose their gross papillary form and become solid. In the course of time they can infiltrate the muscle layer and penetrate the perivesical tissues Lymphatic or vascular metastases may also be found, but spread is mainly along the mucous or submucous lining and by bulky proliferation into the cavity of the bladder itself

On the other hand there is the *solid tumour*, nodular in cystoscopic appearance, usually single and localised. Its tendency is to infiltrate the underlying muscle early, to invade lymphatics and blood-vessels, and in time to become fixed to the pelvic wall It has a higher intrinsic malignancy than the papillary tumour and it must be caught early if it is to be cured.

Stage

The extent of penetration into or through the bladder wall determines the stage of the disease, it is important in assessing operability and prognosis It can only be told with certainty after the whole thickness of the wall, or the whole bladder, has been removed, but a fairly accurate clinical assessment can be made on bimanual examination under full anæsthetic relaxation I have grouped all my cases in which staging was possible into groups A, B, and C corresponding with the mucosal, muscular, and perivesical stages of infiltration

Grade

Another pathological feature which influences the behaviour of bladder cancer is the histological degree of malignancy, known as the grade of the tumour For many years we have followed the system, described by Dukes and Masina (1949) of recognising three such grades—low, medium, and high. Though there is a correlation between grade and stage, the grade of malignancy is more important in the papillary tumours, whilst the stage of penetration gives most information in the solid growths

Rare Forms

Pure squamous-cell growths occur, apart from tumours which show areas of squamous metaplasia and primary columnar-cell adenocarcinomas may arise from the urachus or from the mucous glands of the base There are 3 cases of sarcoma in this series

Diagnosis

Hæmaturia is the outstanding clinical feature of cancer of the bladder in this series it was present in 97% of over 500 patients In secondary growths, due to extension from other viscera, the proportion of patients with hæmaturia was 75% Occasionally the first symptoms are those of cystitis with frequency and pain, but the urine is often sterile

Cystoscopy with a small examination cystoscope under a local anæsthetic usually suffices to establish the diagnosis, but the investigation should always be repeated under a general anæsthetic with an instrument with a good irrigating channel, a clear wide-field telescope, and plenty of time

The excretion pyelogram will show whether the upper urinary tract is normal, a dilated ureter above a growth usually indicates infiltration. A "bite" deformity in the cystogram is suggestive of a solid growth, whilst a papillary tumour can be recognised by the irregular distribution of the medium between the fronds The size of the tumour can be assessed with reasonable accuracy from the X-ray pictures

At the time of cystoscopy a piece of the growth should be removed for biopsy, and the empty bladder should always be examined bimanually under full relaxation A tumour of average size is palpable, a solid tumour is firm and may be mobile or fixed, a papillary tumour is softer and more often mobile within the bladder A firm easily palpable tumour indicates infiltration of the bladder wall The urine should be examined bacteriologically

Treatment

Guiding Principles

New types of treatment continue to appear and the clinician must be constantly ready to change his method of attack I believe that the greatest hope at present lies in the combination of surgery and radiotherapy The collaboration between the two must be a true partnership for the benefit of the patient, and in no sense must it be competitive Perhaps when our concepts of ætiology are further clarified our treatment will become partly biochemical.

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* Based on the first of three Lettsomian lectures for 1958 delivered before the Medical Society of London. The full text will later appear in the *Transactions* of the society

If the disease is one which affects the whole bladder, then treatment should in theory be by total cystectomy or total irradiation As it is the papillary growth which has this tendency most, one might make a case for total cystectomy or irradiation for all papillary tumours Yet experience shows that if such tumours are not extensive when first seen they can be kept in control by local treatment, and some do not recur 70% five-year survival can be obtained by cystodiathermy alone in papillary carcinoma of low malignancy, but the high recurrence-rate shows the widespread liability to the disease

Solid growths, on the other hand, more often appear as single lesions If seen early and in an accessible position they can be removed by partial cystectomy or segmental resection with good prospect of success Too often, however, they have reached the stage of perivesical or distant spread, or they are of high malignancy. In such cases control is unlikely, whatever the method of treatment, though considerable palliation can be given by supervoltage X-ray therapy

Radiosensitivity is directly proportional to the degree of malignancy, and the finding of a high degree in a papillary tumour should be an indication to introduce some form of irradiation into the treatment Whilst conventional (200 kV) therapy has a limited value, the possibilities of the supervoltage machines are much greater (Busby 1957, Swinney 1957, Cavazzana 1957) I am fortunate in having the collaboration of Professor Windeyer with the large machines at Mount Vernon Hospital Our two-year experience with them is too recent for the presentation of results in detail, but we can report a satisfactory regression in papillary tumours and better palliation in the infiltrating growths than by any other method

Though supervoltage therapy has the great advantage of producing little general reaction and only slight skin changes, one untoward result of any form of effective irradiation is the production of telangiectases in the bladder These small vessels have a tendency to bleed, arousing a suspicion of recurrence Light cystodiathermy may check the bleeding, but too deep coagulation may make it worse Another occasional unpleasant sequel is radionecrosis and a contracted bladder, it is more common if the treatment has been given too quickly I have seen it in 2 cases treated by intracavitary irradiation with a solid bead of cobalt-60, both of which needed cystectomy, and in 2 whose growths were very effectively treated by Mr Wallace with intracavitary liquid isotopes

Diversion of Urine

Urinary diversion is necessary before total cystectomy and must be seriously considered before radical X-ray treatment Ureterocolostomy has fallen somewhat out of favour owing to the risk of acidosis, but ureteroileostomy, which is free from this risk, carries the need to wear a receptacle for the urine Though most patients manage the receptacle well, I feel that there is still a place for ureterosigmoidostomy with proper electrolyte control

I have also done palliative urinary diversion in 50 cases, and palliative cystectomy, where the growth was already beyond the bladder, in another 34 9 further patients were deemed untreatable by surgery or by irradiation when first seen Of these 93 patients, for whom there was no real hope of cure, 16 lived for more than a year, 1 lived and worked for seven years after cystectomy, before dying from metastases, and 1 remarkable man is still alive and working more than eight years after ureterocolostomy followed by excision of the dome of the bladder and the insertion of radium needles into an anaplastic carcinoma that was adherent to the pubes Palliative surgery in th disease will not give good statistics but it will prolong life in comfort

Choice of Treatment

For the potentially controllable case there is a w choice of treatment, but we must realise that tables results compare not so much the merits of differe methods as the different types of growth encountere Good results are an indication that the right type treatment was chosen for that particular growth b results show that either the wrong treatment was chose or that the tumour had a very high intrinsic malignanc or that it was too far advanced when first seen Th choice depends on the general condition and renal fun tion as well as on the type, size, situation, multiplicity, a extent of the tumour, and on the presence of muco changes beyond it

PAPILLARY TUMOURS

Cystodiathermy

For localised, pedunculated, papillary, differentiat growths of small or moderate size my preference is f coagulation diathermy with removal of any residual stun by the resectoscope or biopsy forceps

The usual small bladder electrode is insufficient, except f small tumours, and I have found that a modification of Kidd cystoscope increases the range of the operation enormousl The instrument ends in a big ball electrode it has a wide fie of vision, and, of greatest importance, the same large irrigati fitting as the standard cystoscope Tumours of considerab size can be destroyed at one sitting, and it is the first treatme which matters most Repeated nibbles at the surface with small electrode are unsatisfactory and may be harmful

Endoscopic treatment was used in 153 cases, and th five-year survival-rate is shown in table I

TABLE I—FIVE-YEAR SURVIVAL-RATE AFTER TREATMENT BY CYSTODIATHERMY

—	No	5-year survival
Low grade or stage High grade or stage	112 (73%) 41 (27%)	43/60 (72%) 8/25 (32%)
Total	153	51/85 (60%)

Operative mortality, 1/153 (0 6%) *10-year survival, 13/40 (33%)*

Survival for any given period does not tell the whol story, for 75% of these patients needed more than on session of treatment The so-called recurrence-rate ofte represents residual tumours it appears to be lessenin since the adoption of the big-ball cystoscope during th past two years Distant metastasis is uncommon from low-grade tumour, but it can occur at any time

Open Diathermy Excision

In patients with papillary tumours too large for cysto diathermy, or who are unfit for total cystectomy, th bladder can be opened and the growths excised down t the muscle The method was also used for a time, wrongl as we now think, for inoperable high-grade or infiltratin tumours in them it affords poor palliation In any cas spill of urine or tumour is a danger that must be avoided In the low-grade but extensive cases the survival i remarkably good so long as regular follow-up cystoscopic and diathermy treatment are carried out

Of the 28 patients treated in this way 3 subsequently need total cystectomy, 1 of whom is alive ten years later Ther have been 7 five-year survivors and 3 ten-year survivors There was 1 operative death

Excision of Mucosa

As a variant of open diathermy excision I have on 2 occasions excised the mucosa of the bladder

A woman of fifty-eight had extensive papillomatosis I removed the whole area down to muscle with the diathermy needle but left a little apparently normal mucosa on the trigone and around the ureteric orifices In over two years she has had two small recurrences, but the mucosa has regenerated completely Histologically the tumours were papillomata

The other patient, a man of sixty-one, had cystodiathermy in 1952 and 1953 for a low-grade non-infiltrating papillary carcinoma with some squamous metaplasia He defaulted until 1957 when he returned with a bladder full of papillary growth In October, 1957, I excised the entire mucous membrane of the bladder A month later the bladder had a more normal appearance on excretion urography, but he had hourly frequency A cystogram at two months, whilst showing a smooth bladder outline, also showed a bilateral ureteric reflux Three months after operation cystoscopy showed for the most part a pale trabeculated bladder with no apparent mucosa There were some red areas where mucosa appeared to have regenerated, and biopsy confirmed this There was no recurrence of growth but the capacity was only 3 oz The bladder was distended by a balloon to $7^1/_2$ oz This caused considerable bleeding which lasted for twenty-four hours but resulted in some improvement of his frequency It is still possible that he will have to undergo urinary diversion

TABLE II—FIVE-YEAR SURVIVAL-RATE AFTER TREATMENT WITH RADON SEEDS

Grade	No	5-year survival
Papillary differentiated	49	26/37 (*70%*)
Poorly differentiated	33	12/24 (*50%*)
Anaplastic	18	5/12 (*42%*)
Total	100	43/73 (*59%*)

Operative mortality 4/100 (*4%*)

I cannot recommend this operation yet but recent American work on dogs had shown that, after mucosal denudation, bladder contracture and ureteric reflux do not occur if a cuff of mucosa is left around the ureteric orifices (Sanders et al 1958) My 2 cases confirm this observation

Intravesical Implantation of Radioactive Material

When a papillary tumour is of high-grade malignancy, its chances of recurrence after cystodiathermy are high, and a better result can be expected from an implant I have used radon seeds since 1946, but in 1956 I changed to gold grains irradiated in the atomic pile The effect of the two appears to be the same Irradiated tantalum wire can also be used and, since it has a half-life of 112 days, some can be kept in stock I believe, however, that it is more often followed by radionecrosis than the other two substances Insertion is preferably done by open operation the implant is permanent and the bladder can be closed I have used radon seeds in exactly 100 cases (table II).

The local result of radon implantation in an anaplastic growth may be excellent, but it may not prevent distant metastases in the liver and aortic glands

On comparing five-year survivals there is nothing to choose between cystodiathermy and radon implantation in respect of low-grade tumours In high-grade tumours radon shows an appreciable gain Treatment for recurrences was necessary in 75% of the diathermy cases and only in 42% of the implants

Cystectomy

Although partial cystectomy is sometimes suitable for large papillary tumours, there are often mucosal changes, or even small tumours, remote from the main growth, and these make total ablation the better procedure For extensive or multiple papillary tumours total cystectomy offers the best prospect of complete control It carries the added risk of deviation of the urine, and it should not be left to be undertaken as a last resort, as so often happens The operation has its best results in tumours of low malignancy (table III) The newer forms of radiotherapy have got to prove themselves before it can be abandoned

TABLE III—FIVE-YEAR SURVIVAL-RATE AFTER TOTAL CYSTECTOMY

Group	No	5-year survival
A (mucosal)	37	11/28 (*39%*)
B (muscular)	39	3/31 (*10%*)
C (perivesical)	34	1/24 (*4%*)
Total	110	15/83 (*18%*)

Operative mortality, 14/110 (*12 7%*)

The statistical results of total cystectomy appear poor, but the operation is generally used for the most extensive cases of papillary tumour Of the 11 patients in group A who passed the five-year mark 10 are still living and 1 died from heart-disease after eleven years Muscular penetration worsens the prognosis considerably, and when there is perivesical extension the operation should be regarded as palliative

SOLID TUMOURS

Localised solid nodular tumours, the "bun" carcinomas—if they are not too large, if they do not involve the bladder base, and if there are no mucosal changes elsewhere—are best treated either by partial cystectomy or by extravesical radium implantations

Partial Cystectomy

The excision must be generous and include the whole thickness of the bladder with a patch of peritoneum Mucosal changes beyond the tumour determine the need for total cystectomy In my experience this type of bald tumour is getting less common than the mixed solid and papillary type of high-grade malignancy with infiltration (table IV)

TABLE IV—FIVE-YEAR SURVIVAL-RATE AFTER PARTIAL CYSTECTOMY

Group	No	Survival	
		10 years	5 years
A (mucosal)	17	3/9 (*33%*)	7/12 (*58%*)
B (muscular)	56	9/32 (*28%*)	16/44 (*36%*)
C (perivesical)	15	0/6 (*0*)	0/6 (*0*)
Total	88	12/47 (*26%*)	23/62 (*37%*)

1 sarcoma survived $6^1/_2$ years Operative mortality 6/89 (*6 7%*)

Chances of survival at ten years and at five years diminished with increasing depth of penetration of the bladder wall only 2 patients with perivesical extension lived for more than one year Those with muscle penetration predominated, and survival of 28% at ten years was surprisingly good The most favourable site is the dome There were 4 cases of urachal tumour in which the umbilicus and urachus were excised en bloc with the bladder tumour 1 is still living over twelve years later For tumours near the ureteric orifice there should be no hesitation in reimplanting the ureter This was done in 14 patients and only 2 kidneys were lost The longest survivor, now eighty years old, was operated upon more than twenty-one years ago and had the ureter reimplanted At no period, however, can one speak of "cure" New tumours, the so-called recurrences, may come at any time Mostly they are of the same grade as the original, but a different tumour may appear

Radium Implantation

Because of the severe and prolonged cystitis which affects the bladder if it cannot be immediately closed, the implantation of radium needles from the inside is out of favour Higham (1955), however, has devised an ingenious method of application on a rubber mould which does allow closure In accessible solid tumours it is possible to implant radium from outside without opening the bladder When high-grade malignancy indicates the need for irradiation this is an alternative to partial cystectomy I have treated 15 patients in this way, all but one with high-grade solid tumours The longest survivor is still living after nearly five years Even if not curative the local irradiation may make the tumour operable

Intracavitary Irradiation

Much—perhaps too much—was hoped from a method which promised uniform irradiation of the whole bladder from a central source The results of treatment are shown in table v Cobalt 60 was used in 11 cases and radium in 2

TABLE V—RESULTS OF TREATMENT WITH INTRACAVITARY IRRADIATION

Lived 3–5 years	4
Lived 1–2 years	6
Lived less than 1 year	2
Operative mortality	1

The only real successes were in non-infiltrating papillary tumours, and the method has now been abandoned

MISCELLANEOUS TUMOURS

In the series there were 11 cases of growth in a diverticulum Most of these are of high grade and infiltrate quickly through the thin wall of the sac, becoming fixed In 32 cases the bladder was invaded from some other viscus in 13 the primary growth was in the uterus or ovary, in 4 in the large intestine, and in 15 in the renal pelvis or urethra Sometimes wide excision of two invaded viscera is possible, and occasionally a pelvic clearance is indicated The cure of a vesicovaginal fistula is always worth while

3 cases of sarcoma were treated by combined irradiation and surgery, 1 lived for eight years, 1 for six and a half, and 1 is living at nearly four years

Conclusions

I have tried to indicate that cancer of the bladder exists in two principal forms The papillary differentiated growth can be relatively benign and readily controlled the solid anaplastic tumour is always very malignant

Duplicity in the more worldly sense is evident from the insidious clinical onset and the late recurrences of the disease The prognosis may appear to depend more on the type of growth than on the treatment, but the disease does at least run true to form It will give early warning of its potential malignancy if the patient is fully examined and carefully assessed

REFERENCES

Busby, S M (1957) *Canad J Surg* 1, 69
Case, R A M (1956) *Brit J prev soc Med* 10, 172
Cavazzana, P (1957) *Urol int* 4, 311
Dukes, C E, Masina, F (1949) *Brit J Urol* 21, 273
Gohgher J C, Dukes, C E, Bussey, H J R (1951) *Brit J Surg* 39, 199
Higham, A R C (1955) *Brit J Urol* 27, 211
Macalpine, J B (1947) *Brit J Surg* 35, 113
Rehn, L (1895) *Arch klin Chir* 50, 588
Riches, E W (1957) *Brit med J* ii, 407
— Page, B H (1956) *Brit J Urol* 28, 258
Sanders, A R Schein, C J, Orkin, L A (1958) *J Urol* 79, 63
Scott, W W, Boyd, H L (1953) *ibid* 70, 914
Swinney, J (1957) *Brit J Urol* 29, 241

THE MEASUREMENT OF THE PREVALENCE OF ISCHÆMIC HEART-DISEASE

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EVIDENCE from death-rates, autopsy studies, and hospital and clinicians' records suggests that the amount of ischæmic heart-disease differs in different communities (Keys and White 1956) Such evidence has been invaluable in suggesting hypotheses about the ætiology of the disease which require testing quantitatively in more representative samples of the population

Of the two epidemiological indices of morbidity, one would prefer to know the attack-rate (inception-rate or incidence) or rate of appearance of ischæmic heart-disease in the community This, however, is difficult to measure, because it needs a detailed follow-up of a large, fully examined, and well-defined group The alternative index, prevalence (i e, the proportion with ischæmic heart-disease in the community at a given time), is an essential preliminary measurement for establishing attack-rates, is more readily determined, and is the one considered in this paper

In the United States the measurement of both these indices is in progress, and preliminary results have been published (Dawber et al 1957, Doyle et al 1957, Chapman et al 1957, Epstein et al 1957, Drake et al 1957) These admirable studies are open to possible criticism, however, on the ground that, although attention is always paid to diagnostic criteria, reproducibility of these criteria has not been investigated, and consequently it is impossible for others, obtaining different values for the prevalence of ischæmic heart-disease in other populations, to know whether they are dealing with an artefact or a true epidemiological difference

Both Doyle et al (1957) and Chapman et al (1957) studied groups of Civil Service employees, the former in New York State, the latter in Los Angeles, while Epstein et al (1957) investigated New York clothing workers Such working populations are not necessarily representative of the whole community from which they were drawn, since, apart from occupational self-selection and social class, those who may have retired because of ill health are automatically excluded Lastly, bias could have been introduced by the rather high refusal rates in Framingham (31%) (Dawber et al 1957), and Los Angeles (25%) (Chapman et al 1957)

Hence there seems to be a real need for techniques for measuring ischæmic heart-disease in unselected populations and ensuring comparability of the medical indices used We discuss these two problems, using material from a survey of representative occupational samples of two communities

Prevalence is essentially a ratio—in the present context the ratio of those suffering from ischæmic heart-disease to the population at risk Difficulties and errors may arise, therefore, not only in identifying the cases of ischæmic heart-disease but also in defining, sampling, and measuring the community from which they are drawn The latter problem is usually neglected—partly because its importance is not appreciated, but partly perhaps because people are secretly rather frightened of it

Measurement of the Population at Risk

Our method has been to define a geographical area, enumerate the inhabitants by a private census, and then carry out a chest X-ray survey (Cochrane et al 1955, Cochrane, Miall, and Clarke 1956) The information thus obtained is transferred to punch cards from which samples can readily be drawn

The first of the two surveys of ischæmic heart-disease was made in 1954 on a random sample of miners and ex-miners living in the Rhondda Fach, a mining valley in South Wales (Thomas et al 1956) The second survey was designed to achieve an occupational contrast An agricultural area, the Vale of Glamorgan, which is 15 miles from the Rhondda Fach, was chosen, and in 1956 a random sample of men aged 55–64 who lived in this area and had never been miners was investigated

Those who appeared in the sample were visited by members of the epidemiological team at the Pneumoconiosis Research Unit and persuaded to cooperate The vast majority were transported either to the unit or to a centre in Cowbridge, in the Vale of Glamorgan, where the examination took place The " response " rate and other details are shown in table I

The first survey was a pilot investigation in which the sample was limited to 55 men In retrospect we consider this too few, and in the second survey we increased the sample to 100 Certain problems are introduced by the measurements being made some time after the nominal census The sample will inevitably include some people who have died or left the area in the interval We have not attempted to substitute others for these, but we have carefully investigated the cause of death in the former and have excluded the latter from the population at risk

TABLE I—RESPONSE-RATE IN THE TWO SURVEYS

Area	No in sample	No left area	No dead	No of refusals	Response-rate of those still in area and still alive
Rhondda Fach	55	2	2	4	47 (*92%*)
Vale of Glamorgan	100	4	1	10	85 (*90%*)

The other source of error relates to the proportion of the sample responding to our persuasion The percentages shown in table I are high They could, of course, be higher, but at present we know of no technique for reducing the refusal-rate below 5–10% Possibly others will discover one

Measurement of the Number with Ischæmic Heart-disease

The diagnosis of ischæmic heart-disease is usually based on clinical, radiological, and electrocardiographic evidence Analysis of the results of the first survey suggested strongly that the electrocardiogram was by far the most important factor in making the diagnosis, that the clinical examination was sometimes valuable, and that the posteroanterior chest X-ray was relatively unimportant Further investigation shows that there is considerable variation in the diagnosis Comparison of the conclusions of several cardiologists, based on clinical and electrocardiographic examination of all members of the sample, would have been desirable, but this proved impossible and we have had to compromise In both surveys we have arranged for the same clinician to make a diagnosis on the clinical and electrocardiographic evidence In addition, all the electrocardiograms have been interpreted by two other cardiologists

Our two main problems have been (1) the difficulties of obtaining satisfactory electrocardiograms and (2) the difficulties associated with different interpretations of the same tracing

Technically perfect electrocardiograms are harder to obtain under survey conditions than in hospital—partly because time is limited and partly because it is difficult or impossible to recall a member of the sample in order to repeat the investigation In neither of our surveys were the electrocardiograms perfect but in the second survey they were much better than in the first, and in a more recent survey they were nearly up to the best hospital standard There is, in addition, the question of which leads and how many should be taken to satisfy different cardiologists In future we intend to take the 12 standard limb and chest leads Our experience also suggests that a direct-writing electrocardiograph has considerable advantages over one recording photographically Unsatisfactory tracings can be immediately repeated before the subject departs, and additional leads can be added at the discretion of the cardiologist making the clinical examination

The differences of interpretation presented a more serious problem Photographic prints of the electrocardiograms from the two surveys (concealing the origin of the tracings) were mixed at random and read independently by each of the three cardiologists, who were asked to record their observations on a standard form The cardiologists* reported on the tracings as they would have done in ordinary clinical practice They *held no prior discussion on the criteria for diagnosing* ischæmic heart-disease The diagnostic criteria used by the third observer (A J T) were those detailed previously (*Thomas et al 1956*) and we expected that those used by the other two readers would be broadly similar The results are shown in table II It is clear that there were considerable differences of interpretation The commonest cause of disagreement was the borderline tracing, next was the difficulty of differentiating cardiac hypertrophy, with or without associated strain, from ischæmia, and lastly, some differences may have been due to unsatisfactory tracings and to the wording of the form (but exclusion of the unsatisfactory electrocardiograms did not produce any significant improvement) In future surveys we shall use a more precise form Observer differences might be further reduced by preliminary discussion of precisely what abnormalities are to be accepted for diagnosis

In view of the observer differences we have adopted two indices for the analysis of the results When the diagnosis of ischæmic heart-disease has been reached on complete clinical, radiological, and electrocardiographic assessment, we speak of the " clinical " index, when we have used those electrocardiograms which all three observers regarded as showing ischæmic heart-disease we speak of the " electrocardiographic " index The advantage of the first index is the use made of the valuable information supplied by the clinical examination Its main disadvantage is the difficulty, in comparative studies, of preventing possible bias through the clinician knowing the area from which the subject comes The advantage of the " electrocardiographic " index is the ease with which such bias can be avoided

Results

Prevalence in the Two Areas

If we restrict ourselves to the two indices we can compare the prevalence of ischæmic heart-disease in the two

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* J F Goodwin, physician, Postgraduate Medical School, Hammersmith, L G G Davies, senior medical registrar, National Heart Hospital, and A J Thomas, physician, United Cardiff Hospitals

TABLE II—PREVALENCE OF ISCHÆMIC HEART-DISEASE DIAGNOSED CLINICALLY AND/OR ELECTROCARDIOGRAPHICALLY IN THE TWO COMMUNITIES BY VARIOUS READERS

—	Vale of Glamorgan (85 cases)	Rhondda Fach (47 cases)
Diagnosed clinically (clinical index)	19 (*22%*)	18 (*38%*)
Diagnosed electrocardiographically		
By all 3 readers (electrocardiographic index)	12 (*14%*)	10 (*21%*)
By 2 of the 3 readers	6 (*7%*)	2 (*4%*)
By 1 of the 3 readers	16 (*19%*)	10 (*21%*)
Total (by any of the 3 readers)	34 (*40%*)	22 (*47%*)
Corrected * clinical index	22 (*25%*)	18 (*38%*)
Corrected * electrocardiographic index	15 (*17%*)	10 (*21%*)

* When the 3 additional Vale cases are included

populations, as shown in table II This, however, is not entirely satisfactory

Among those who refused examination there were 2 in the Vale of Glamorgan who had been diagnosed in hospital as suffering from ischæmic heart-disease and whose electrocardiograms were reviewed by one of us (A J T) It was impossible to include their electrocardiograms in the series sent to the three readers, but we think that they should be added to both indices The case of the man who appeared in the sample but died of ischæmic heart-disease before the survey presents a somewhat different problem, but we believe that he too should be included in both indices The effect of these additions is shown in table II The difference between the two areas is much reduced

We conclude that we have not been able to prove the existence of a significant difference in prevalence of ischæmic heart-disease between the two areas The possibility of its existence has not, of course, been excluded

Characteristics of Populations in Relation to the Disease

Another advantage of this type of prevalence study is the opportunity it gives of comparing those with ischæmic heart-disease with those of the same age and sex living in the same area without ischæmic heart-disease Such a control group is clearly preferable to the more usual one, drawn from hospital patients

Personal and anthropometric characteristics (table III)—There was little difference in either area in the average age of the ischæmic and control groups Both indices showed a considerable difference in average weight between the two groups, and smaller differences in standing and sitting height, and in nearly all cases the "electrocardiographic" index, which probably indicates the more severe cases, gives a greater difference than the "clinical" index Arm girth and arm skinfold measurements were available only for the Vale population The results suggest that the higher average weight of those with ischæmic heart-disease is more likely due to muscle than to fat

TABLE III—ANTHROPOMETRIC CHARACTERISTICS

—		Vale of Glamorgan		Rhondda Fach	
		Ischæmic heart-disease	Others	Ischæmic heart-disease	Others
No in group	E C G	12	73	10	37
	Clinical	19	66	18	29
Age (years)	E C G	58·6	59 5	61 0	60 6
	Clinical	59 7	59 3	61 1	60 6
Standing height (inches)	E C G	66 9^{1}	65·6	66 7	66 2
	Clinical	66 0	65 7	66 6	66 0
Sitting height (inches)	E C G	35 3^{3}	34 6	34 7	34·4
	Clinical	34 8	34 7	34 7	34 4
Weight (pounds)	E C G	166 3^{2}	150 2	156 8	138 8
	Clinical	160 2	149·9	156 9^{4}	133 8
Arm girth (inches)	E C G	10 7	10·4		
	Clinical	10 6	10 4		
Arm skin fold (cm)	E C G	8 8	9 3		
	Clinical	9 5	9 2		

1 0·015>P>0·01 2. P<0·001 3 0·015>P>0·01 4 0·005>P>0·001

Physiological and biochemical factors (table IV)—The raised blood-pressure and the indirect maximum voluntary ventilation (M V V) in those with ischæmic heart-disease have been previously described (Cotes et al 1956) One point of interest is the decreased difference in systolic blood-pressure when the "electrocardiographic" rather than the "clinical" index is used This was due to the difficulty of diagnosing ischæmic heart-disease in the presence of left ventricular preponderance, which led to disagreement between observers Our findings about height are also of interest in relation to the higher M V V in the group with ischæmic heart-disease The increased height is found both for total height and stem height, and probably accounts for some of the difference in *M V V* The data about cholesterol are being published elsewhere (Morris, to be published) The difference (*11 ± 14 6 mg per 100 ml*) between those with and those without ischæmic heart-disease is small and statistically insignificant

TABLE IV—PHYSIOLOGICAL AND BIOCHEMICAL CHARACTERISTICS

—		Vale of Glamorgan		Rhondda Fach	
		Ischæmic heart-disease	Others	Ischæmic heart-disease	Others
Average systolic blood-pressure (mm Hg)	E C G	168 3	160 1	156	145
	Clinical	180 8^{2}	155 7	165 8^{4}	139 4
Average diastolic blood-pressure (mm Hg)	E C G	96 3^{1}	87 2	86	82
	Clinical	96 3	86 2	89 4^{4}	80 7
Average M V V (indirect) (litres per min)	E C G	101 7^{3}	87 0	81 4	70 7
	Clinical	87 1	89 7	84 5^{5}	65 8
Average blood-cholesterol (mg per 100 ml)	E C G	260	249		
	Clinical	256	250		

1 Diastolic 0 02>P>0 01 2 Systolic 0·002>P>0·001
3 0 04>P>0 03 4 Systolic P=0 004 Diastolic 0 04>P>0 03
5 P=0 01

Family data—The information in table V was obtained from the members of the samples at the time of the examination in the case of the Vale of Glamorgan, and two years later in the case of the Rhondda Family size appears not to be correlated with ischæmic heart-disease, for the results differ in direction in the two surveys The survival rate of the fathers of those with ischæmic heart-disease seems unexceptional they appear to do rather better than the fathers of the controls Conversely, the mothers of the ischæmic heart-disease group do rather worse than the mothers of the controls, but the differences are not significant The most striking results come from the brothers and sisters In every comparative pair there is a higher mortality among the siblings of the group with ischæmic heart-disease The pairs where the differences are statistically significant are indicated in the table

The causes of death of brothers and sisters have been investigated in both areas, but with such small numbers it is very hard to draw any conclusions as to the causes of the excess mortality

Other factors—In the paper reporting the survey of ischæmic heart-disease in the Rhondda Fach an attempt was made to test the hypothesis advanced by Morris et al (1953) that hard manual work reduces the risk of developing the disease The average number of years at the coal face in the two groups was compared, on the assumption

TABLE V—FAMILY DATA

—			Vale of Glamorgan		Rhondda Fach	
			Ischæmic heart-disease	Others	Ischæmic heart-disease	Others
Family size		E C.G	6 4	5 2	4 8	5 6
		Clinical	5 8	5 3	4 8	5 8
Survival of fathers	% dead	E C.G	91 7	97 8	100	100
		Clinical	94 7	90 9	100	100
	Average age at death	E C.G	69 1	68 5	69 7	63 6
		Clinical	69·0	68 5	67 3	59 0
Survival of mothers	% dead	E C.G	100	86 3	100	100
		Clinical	100	84 8	100	100
	Average age at death	E C G	65 7	66·0	61·5	68·5
		Clinical	65 8	66 0	65 4	67·9
% of brothers dead		E C.G	36 8	28·4	63 2	42 0
		Clinical	40·0	26 2	60·6	38 3
% of sisters dead		E C.G	55 6[1]	20 7	52 6[2]	19 3
		Clinical	41 5	21 3	38 9[3]	18 2

1 P<0 001 2 P<0·01 3 P=0 045

that coal-face work is on the average harder than other work in a mine, but no significant difference was found The material has now been reanalysed using the "electrocardiographic" index Those diagnosed electrocardiographically as having ischæmic heart-disease had worked for 5 7 years on the coal face compared with 16 9 years for the controls The difference of 11 2 years is statistically significant (0 005>P>0 001) This, in general, supports Morris's hypothesis, but the results could be due to men with heart-disease leaving the coal face early, or to some other type of occupational selection.

We have also some information about mean chest diameter This was measured on a high proportion of the miners and ex-miners in the Rhondda during the first Rhondda Fach survey Using the clinical index, the mean chest diameters of those with and without ischæmic heart-disease was 27 8 cm and 26 9 cm, and using the electrocardiographic index the figures were 28 1 cm and 26 5 cm

The material has also been analysed as regards smoking habits and social status (using the Registrar General's classification), but no significant correlations have emerged.

Discussion

Measurement of Prevalence

The essential difficulty in comparing the prevalence of ischæmic heart-disease in different areas is to avoid bias due to preconceived hypotheses The electrocardiogram is the only suitable means of ensuring that such bias is eliminated Tracings from different areas can be mixed and read by observers who are not told where they come from In such circumstances the precise level of diagnosis of ischæmic heart-disease is relatively unimportant since the criteria adopted can be assumed to be the same for all the tracings, comparisons between areas or between occupations will be valid Hence we believe that our comparisons in the present paper are justified On the other hand the wide variation in interpretation of electrocardiograms makes us sceptical of our absolute values for the prevalence of ischæmic heart-disease, and shows that much more work must be done before the findings of workers in different centres can be justifiably compared Though the differences may disappear under the impact of the discussion caused by their measurement more basic research is likely to be needed. This will include the correlation of clinical and electrocardiographic findings with post-mortem findings on unselected groups, and the follow-up of large unselected populations to determine the relation between electrocardiographic abnormalities and expectation of life

Ætiology of Ischaemic Heart-disease

A widely entertained hypothesis relates ischæmic heart-disease to the fat content of the diet and to the blood-cholesterol (Keys 1955, Bronte Stewart et al 1955) There is evidence from many countries that people who live on diets low in animal fats tend to have a low mean serum-cholesterol level and little liability to ischæmic heart-disease (Keys and White 1956) While certain discrepancies in this hypothesis have been noted (Morris 1956, Yudkin 1957), the relevance of the blood-cholesterol to ischæmic heart-disease is supported by the observation at Framingham (Dawber et al 1957) that people with a high total blood-cholesterol were more liable to an episode of ischæmic heart-disease

In our investigation of men aged 55-64 the mean serum-cholesterol was insignificantly higher in those with ischæmic heart-disease than in the controls This is at variance with the findings of Gertler and White (1954) in young adult males Though racial differences between the groups studied—as demonstrated between Italians and Jews in the clothing workers' survey (Epstein et al 1957)—might account for this discrepancy, a more probable explanation is that over the age of 55 we are dealing with a survivor population those who had a high blood-cholesterol in their 30s and 40s had already died of ischæmic heart-disease. Alternatively, disordered lipid metabolism may be important mainly at younger ages Biorck et al (1957) concluded that, in people under 50 years old, the serum-cholesterol was higher in those with myocardial infarction than in normal controls, but over this age the difference was insignificant

The differences in blood-pressure and maximum voluntary ventilation (indirect) have been discussed previously (Thomas et al 1956, Cotes et al 1956) Since then, Epstein and his coworkers (Epstein et al 1957) have confirmed the raised blood-pressure in Italians with ischæmic heart-disease in New York, but not in Jews As we have also found a significant relation between ischæmic heart-disease and body-weight, and weight is related to blood-pressure (Master et al 1950), one must be cautious in drawing conclusions

Our anthropometric results are of greater interest Gertler and White (1954), who give a good summary of the literature, found that among young males those with coronary disease were significantly shorter and lighter The striking difference between their results and ours is possibly explained by their dealing with young males Alternatively, some bias may have been unintentionally introduced when selecting the 146 unmatched controls to compare with the 97 coronaries Epstein (Epstein et al 1957) apparently measured the heights of his population, but does not comment on any differences between those with and those without ischæmic heart-disease

As regards our family data, the situation is somewhat similar Here too the literature has been well summarised by Gertler and White (1954) They found that the parents of people with ischæmic heart-disease had a higher mortality than the parents of controls For this purpose their material was more suitable than ours, since the younger age-group made the measurement more sensitive They also found a higher mortality among the siblings of the controls (20%) than among siblings of the coronary group (15%), though the difference was not significant

We, on the other hand, found a significantly higher mortality among the siblings of those with ischæmic heart-disease Our data agree with theirs in showing no significant difference in the size of family in the two groups For this study our age distribution is more suitable

Faced with these divergent results we can only conclude that further work is required on similar populations, particular care being paid to the choice of controls

Summary

1 Comparison of the prevalence of ischæmic heart-disease in different places presents certain difficulties

2 The technique of random sampling from a population, accurately defined by private census, is illustrated by two surveys of men aged 55-64 The findings in a sample of 55 miners and ex-miners living in the Rhondda Fach are compared with the findings in a sample of 100 men who had never worked in dusty occupations, living in the Vale of Glamorgan

3 Three cardiologists independently read the electrocardiograms from each subject, and their findings varied considerably Hence, though the comparison of the two areas may be regarded as valid, the absolute prevalence values should be treated with reserve

4 Two indices of ischæmic heart-disease have been used

(1) The clinical index, based on clinical assessment, electrocardiography, and radiography, by one cardiologist

(2) The electrocardiographic index, based on agreement between three cardiologists that an electrocardiogram showed changes compatible with the diagnosis of ischæmic heart-disease

The prevalence in the two areas was

Clinical index Vale 25 0%, Rhondda Fach 38 3%
Electrocardiographic index Vale 17 0%, Rhondda Fach 21 3%

Though the mining group seemed to have a somewhat higher prevalence the difference was not statistically significant

5 Those diagnosed as having ischæmic heart-disease were both taller and heavier than the others

6 The siblings of the men with ischæmic heart-disease had a higher mortality than the siblings of the controls

7 No significant difference was found in the mean serum-cholesterol levels of the two groups

We wish to thank Dr J F Goodwin and Dr L G G Davies for reading the electrocardiograms, and for their invaluable suggestions, Dr B Bronte Stewart for reading the manuscript, Miss Barbara Snow, of University College, for statistical help, and our colleagues at the Pneumoconiosis Research Unit for their helpful advice and criticism, particularly Dr J C Gilson, director of the unit, Mr P D Oldham, statistician, and Dr T G Morris, who carried out the serum-cholesterol determinations

REFERENCES

Biorck, G , Blomqvist, G , Sievers, J (1957) *Acta med scand* 158, 493
Bronte Stewart, B , Keys, A , Brock, J F (1955) *Lancet*, ii, 1103
Chapman, J M , Goerke, L S , Dixon, W , Loveland, D B , Phillips, E (1957) *Amer J publ Hlth*, 47, 33
Cochrane, A L , Cox, J G , Jarman, T F (1955) *Brit med J* i, 371
— Miall, W E , Clarke, W G (1956) *Tubercle*, 37, 417
Cotes, J E , Higgins, I T T , Thomas, A J (1956) *Brit med J* i, 601
Dawber, T R , Moore, F E , Mann, G V (1957) *Amer J publ Hlth*, 47, 4
Doyle, J T , Heslin, A S , Hilleboe, H E , Formel, P F , Korns, R E (1957) *ibid* p 25
Drake, R M , Bueckley, R W , Breslow, L (1957) *ibid* p 43
Epstein, F H , Boas, E P , Simpson, R (1957) *J chron Dis* 5, 300, 329
Gertler, M M , White, P D (1954) Coronary Disease in Young Adults a Multidisciplinary Study Cambridge, Mass
Keys, A (1955) *J chron Dis*, 4, 364
— White, P D (1956) Cardiovascular Epidemiology, vol 1 New York
Master, A M , Dublin L I , Marks, H H (1950) *J Amer med Ass* 143, 1464
Morris, J N (1956) *Lancet*, i 687
— Heady, J A , Raffle, P A B , Roberts, C G , Parks, J W (1953) *ibid* ii, 1053, 1111
Morris, T G (to be published)
Thomas, A J Cotes, J E , Higgins, I T T (1956) *Lancet*, i, 414
Yudkin, J (1957) *ibid* ii, 155

TREATMENT OF SEVERE HEAD INJURIES

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THE very severe head injury, complicated or uncomplicated by surface hæmorrhage, has always been the cause of grave concern to the neurological surgeon It has been noted that patients with cerebral lesions die in a characteristic way, and Jefferson (1944) wrote

> " It is the fate of all of us to watch patients with cerebral lesions dying from something characterised by tachycardia, and cardiac irregularity, from upsets of thermal regulation, from metabolic upsets which we have not yet found a means to study properly, from something that bears the hallmarks of a disease process as much as, say, pneumonia "

The distinguishing characteristics of the group of cases of head injury to be described here were a partial or complete decerebrate posture with tonic fits and a rapidly rising temperature Other signs of autonomic disturbance were usually present, but fell into no clear-cut pattern likely to be useful in routine diagnosis Kinnier Wilson (1920) described the association of this syndrome with lesions of the upper brain-stem and pointed out its resemblance to the effects of experimental transaction at the level of the superior colliculus in animals Other observers have confirmed and amplified Wilson's description

When the syndrome arises after head injury, *it is* probably the result either of intrinsic damage to the upper brain-stem, or of a mid-brain shift following a rise in supratentorial pressure When it arises as a secondary effect of raised pressure, it occurs late in the process of descent and indicates considerable damage amounting to partial or complete transection, which is not always reversible The signs arise from the paralysis of some structures and the action in isolation of others

Several types of herniation of supratentorial structures into the incisura have been described (Meyer 1920, Vincent et al 1936, Azambuja et al 1956), all of which eventually compress and distort the brain-stem or imperil its blood-supply The mechanics of these processes have been well reviewed by Johnson (1957), who points out that, while compression is often worst at the level of the incisura, structure must be distorted at all levels, and that, whatever the pattern of movement, when the pressure is supratentorial the whole brain-stem will shift down This downward shift may be sudden and catastrophic, but on the other hand it may be gradual, and in the latter case there may be little clinical evidence of the shift until a final and comparatively small further displacement leads to fatal compression

It is difficult clinically to identify accurately the causes of swelling of the brain in any given head injury, but morbid-anatomical and experimental evidence suggests that it is due to a combination of hæmorrhage, local œdema, and hyperæmia with the effects of hypoxia, carbon-dioxide retention, and " acceleration concussion "

Hæmorrhage is often found, and if massive may be the principal cause of displacement Of the cases to be described, in 27 out of 56 in the control series and in 15 out of 26 in the treated series, such hæmorrhage, subdural or extradural, was present Local œdema or its histological effects may be demonstrated in close proximity to lacerations of the brain and sometimes very near to the anterior part of the lateral ventricle This is likely to be only a contributory factor, as it occurs rarely if ever in a massive and generalised form (Greenfield 1938)

Hyperæmia of the brain is found at necropsy after concussion and has been so produced experimentally in cats White et al (1942) demonstrated hyperæmia of the brain in cats after inhalation of increased concentrations of carbon dioxide, and swelling of brain substance not due to hyperæmia in conditions of severe hypoxia Davies and McKinnon (1949) have shown the importance of the combined effect of hypoxia and hypercapnia in producing cerebral hyperæmia in man There is experimental evidence that generalised swelling of the brain which cannot be accounted for by hyperæmia, or correlated directly with water content, occurs after acceleration concussion. White et al (1943) recorded increases in brain volume of up to 5% in cats concussed by the method of Denny Brown and Ritchie Russell (1941)

When a brain-stem shift has occurred, other mechanisms come into play Compression or angulation of the brain-stem can obliterate the aqueduct, causing internal hydrocephalus Trapping of the transtentorial veins in the incisura will cause a rise of venous pressure and impede cerebral blood-flow

Johnson (1957) has drawn attention to the role of respiratory embarrassment in exacerbating downward displacement of the brain-stem by causing distension of intracranial veins Patients with severe head injuries commonly inhale mucus, vomit, and blood soon after injury, particularly if transferred to hospital in the supine position, and pooling of mucus in the pharynx is often observed Apart from these mechanical factors, mid-brain dysfunction itself leads to disorderly respiration In both cases venous pressure inside the skull must fluctuate considerably, and some observations made during the present series point to the importance of respiratory disorder as a precipitating cause of coning

3 patients in the series were admitted in a state of cerebral irritation and coma without focal signs, passed through an episode of mechanical respiratory obstruction, and then assumed a decerebrate posture with rising temperature Subdural hæmatomas were discovered at craniotomy in all 3 cases In these cases the appearances suggest that a large downward displacement existed with few clinical signs until a further slight descent provoked by the respiratory upset tipped the balance and produced a pressure cone

The role of respiratory insufficiency in the mortality of severe head injuries has been discussed by Maciver et al (1958), who outlined the regime which we have adopted, since Dec 13, 1956, in the treatment of such cases The most important features of the treatment are as follows

1 Correct posture to prevent seepage into the lungs and tracheobronchial tubes

2. Isolation of the lungs from the disorganised pharynx by early tracheotomy

3 Their further protection by continued aseptic tracheobronchial toilet.

4 The use of a lytic cocktail to coordinate the reticular mechanisms of the brain-stem, and control rigidity, restlessness, and hyperthermia

5 Avoidance of oral feeding during unconsciousness

6 Maintenance of physiological tensions of oxygen and CO_2 in the blood.

7 Maintenance of fluid and electrolyte balance and calorie intake.

8 Combating of infection by use of antibiotics

9 Relief or prevention of secondary cerebral œdema by use of intravenous triple plasma.

We describe here the details of treatment, the difficulties we have encountered, and the progress we have made Of 83 cases in the present series, 26 were treated by the regime described.

Clinical Features

The clinical picture varied according to the degree of damage or compression to the brain-stem The best prognosis attended the cases showing hyperpyrexia with tonic fits superimposed on decerebrate rigidity The poorest prognosis was present in the cases which showed complete thermolability and absolute flaccidity save when disturbed by feeble tonic fits Medullary failure was imminent in the thermolabile and flaccid group, the blood-pressure falling and the respirations becoming shallow, irregular, and gasping However, 2 patients with this clinical picture have survived The tendon reflexes are increased in the hyperpyrexial and rigid patients, the plantar reflexes are extensor, whereas in the flaccid state neither tendon reflexes nor toe movements can be elicited.

In the fully developed decerebrate state the patient lies with knees and toes rigidly extended and the ankles plantar-flexed. There is spasm of the femoral adductors and pectorals, the arms are pronated and the wrists flexed, while the elbows are held in a position peculiar to that patient which may be either flexion or extension (fig 1)

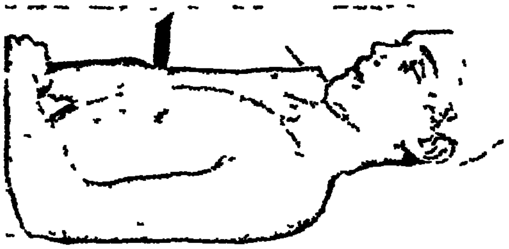

Fig 1—Patient five days after severe head injury, with decerebrate rigidity and hyperpyrexia

Tonic fits, which are merely exacerbations of the spasm described, may be continuous or intermittent They are always associated with a rise of temperature and may be precipitated by external stimulation Partial or fragmentary forms of the decerebrate posture were seen During their recovery 2 patients still showing decerebrate rigidity and pyrexia were able to speak and move the spastic limbs purposefully

A tachycardia of 100–160 developed in all cases within an hour of onset of decerebrate rigidity The breathing was stertorous and the neck veins were distended The patient seemed unable to clear mucus, blood, or vomit from the pharynx (Denny Brown and Ritchie Russell [1941] noted a transient disorder of swallowing mechanisms in concussed cats) In the acute head injury, damage to the vagal nuclei is also partially responsible for this difficulty Vomiting is frequent and usually contains altered blood—sometimes blood previously swallowed but sometimes arising from gastric or œsophageal erosions, which are a common postmortem finding in head injuries of this severity (Maciver et al. 1956) No case of ruptured œsophagus occurred in the treated group, but 2 cases occurred in the control series Absence of bowel sounds were recorded often, abdominal distension occasionally, and retention of urine twice

The pupils were unequal in 16 cases, equal in 6, obscured by orbital hæmatoma in 2, and masked by 3rd-nerve damage in 2 They were reduced in size in most instances and fixed in 19 cases The eyeballs were usually central, but roving movement once, and conjugate deviation twice, have been observed These findings relate to the first examination of the patients

Stage of Coma (one to three weeks)

The signs are a mixture of those due to injury and those due to therapy Muscle hypertonicity is reduced and tonic fits do not occur, the temperature being held steady at 96–98°F Respiration is quiet and free from straining The blood-pressure is usually low on chlorpromazine and tachycardia is constant Weight loss and normochromic anæmia are usual Skin-sensitivity reactions to chlorpromazine and penicillin are often seen, profuse diarrhœa occurred in 4 cases in which tetracycline had been administered The signs of developing bronchopneumonia at this stage are ominous

Stage of Cerebral Irritation

The patient begins to move his limbs purposelessly and thresh around in bed, often screaming in a nerve-racking way The eyes are open and soon appear to be following movements As recovery progresses, movements become more purposeful and noises more like words Pupil size and reactions are normal, and tendon reflexes present and equal in the absence of focal damage, though plantars are often extensor Exceptionally, the decerebrate attitude persists partially (fig 2) Towards the end of this period the patient begins to talk irrationally and can sit up in bed with assistance The tracheotomy has usually healed

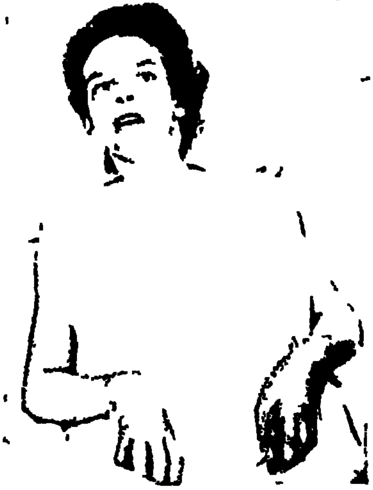

Fig 2—Patient in control series showing persistent decerebrate attitude three months after severe head injury in which brainstem was primarily involved

Stage of Confusion (two to twelve weeks)

This period covers the piecemeal return of mental faculties together with the ability to stand, balance, walk, feed, and make use of the toilet Ability to talk comes early—on the average three weeks after injury—but rational conversation much later The patient is disorientated, often failing to recognise family and friends, and can develop extraordinary delusions to account for his condition and circumstances The average time for walking was six weeks, but 1 patient was mobile after a fortnight When physical recovery outstrips mental, a formidable nursing problem presents The appetite is always excellent and usually ravenous, and weight is rapidly regained Formal neurological examination and assessment of deficit are possible

Treatment

The regime laid down is in no way a substitute for accurate diagnosis and surgery—rather the reverse, for it places within the scope of surgery cases in which the prognosis would otherwise be hopeless A decerebrate picture in a case of acute head injury was always thought in the past to be an unequivocal sign of an injury to the mid-brain In some cases presenting with similar signs, a surface hæmorrhage has been found at operation or at necropsy, Jefferson (1921) drew attention to this fact and suggested that, in any case where a doubt exists, exploratory burr-holes are advisable We would further suggest that routine burr-holes are always advisable to exclude surface collections, particularly subdural hygromas and hæmatomas

Immediate Treatment on Admission

Although speed is not always of prime importance, there are occasions where it is life-saving Where a patient is admitted deeply unconscious in a decerebrate state with inadequate respiratory effort and a rapidly rising temperature, the pupils, long bones, ribs, pelvis, spine, abdomen, and chest should be rapidly examined to exclude fracture, pneumothorax or hæmothorax, and intra-abdominal bleeding

The clothing should then be removed and a drip set up at the ankle 400 ml of sterile water should be mixed with dried plasma of 3 pints of blood, and run as fast as the drip will allow, a specimen of blood for cross matching being obtained at the same time 25 mg of chlorpromazine should be injected into the drip, thus bringing about relaxation in approximately a minute As soon as the jaw relaxes an endotracheal tube should be passed under direct vision, and suction of inhaled blood or regurgitated stomach contents should be instituted, and warm, moist oxygen given A stomach-tube should be passed and the stomach emptied, the tube being retained for further aspirations The head is then shaved and any fractures of the limbs are immobilised The question of tracheotomy and of operation is then discussed, and if this is necessary, it is arranged as soon as the patient's condition is reasonably satisfactory, and as soon as possible regular doses of lytic cocktail are given, usually by drip or by intramuscular injection Apart from triple plasma, blood in our opinion is the only isotonic fluid permissible, and it is given only where associated injuries would necessitate transfusion

The first case treated along these lines was a boy of 16 years, admitted in decerebrate rigidity an hour after being knocked down by a car On admission his temperature was 105 4 F and he was in circulatory failure with Cheyne-Stokes breathing Normally we would have expected death within half an hour, but the use of intravenous triple plasma and intravenous chlorpromazine, exposure to cold air with wet sheets, and the passage of an endotracheal tube changed the picture immediately Within an hour the temperature was brought down to normal and the decerebrate condition was under control When the endotracheal tube was removed a few hours after admission, his condition immediately deteriorated, he became blue and obviously anoxic, and his decerebrate rigidity returned His tube was replaced with immediate improvement, and tracheotomy was carried out as soon as possible with continuing improvement in his condition After five weeks of coma he began to make a satisfactory recovery

Posture

It is important, until at least an endotracheal tube is passed and the stomach contents aspirated, to nurse the patient in the semiprone position with a Trendelenburg tilt of 20°, or even in a knee-elbow position where there is a drainage of blood and cerebrospinal fluid into the mouth and pharynx. Once, however, the patient is intubated or tracheotomy has been performed and the regime commenced, we are of the opinion that the best position for nursing is the supine position without pillows initially, the position being frequently changed, and before suction the patient is placed in the Trendelenburg position for ten minutes to effect adequate drainage. All other positions appear to embarrass respiration. After suction the patient is returned again to the supine position. As the patient progresses a sitting position can be gradually adopted.

Tracheotomy

In the deeply unconscious patient suffering from the effects of a severe head injury, cerebral anoxia is likely to produce profound and irreversible changes in the brain-stem and cerebral hemispheres. In our opinion tracheotomy is the only certain method in the prevention of cerebral anoxia, and in all adult patients it has been our practice to perform this operation as quickly as possible. As has been already indicated, inserting an endotracheal tube may be of value as an emergency procedure, or if early return to consciousness appears likely, but in our opinion no tube should be retained for longer than eight hours. In children tracheotomy may not be as necessary but should be performed at once if indicated. Of 21 adults in this treated series 20 had tracheotomies, but of 5 children only 2 had this operation performed. Once tracheotomy has been performed careful aseptic suction must be applied frequently, and the tracheal tube and bronchial tree must be kept clear. This suction must be adequate but reasonably gentle, and the suction tube should be soft enough to ensure that damage to the lining of the bronchial tree is minimal. The tube should also be long enough to reach to the depths of the tree when required, suction first being applied on one side and the patient then turned so that suction can be applied to the other bronchus. Any oxygen administered should be warmed and moistened so that hardening or coarsening of the secretions is avoided.

The Lytic Cocktail

This cocktail, consisting of chlorpromazine, promezathine, pethidine, and levallorphan, has been used in all cases, but no attempt has been made to produce hypothermia or a hibernating condition.

The cocktail has the following functions:

1. It has made it possible to control temperature with comparative ease, and our aim is to maintain as normal a body temperature as possible.
2. It relieves muscle spasm and abolishes tonic fits, thereby reducing heat production and oxygen consumption.
3. Vomiting is reduced or abolished by chlorpromazine, whilst gastric secretion and intestinal mobility are both markedly reduced, and there is a hope that autonomic disturbance, ulceration and rupture of the œsophagus, or mucosal hæmorrhage may be prevented. Drying of secretions in the mouth and respiratory tract, though a troublesome side-effect in the conscious patient, is highly desirable in the decerebrate state.
4. It enables intubation to be carried out without using a relaxant.
5. It markedly reduces restlessness.
6. It has been found to protect animals against traumatic and hæmorrhagic shock, and Pocidalo and Tardieu (1954) found that it increased survival-time or diminished the severity of lesions produced in dogs by injecting irritant materials into the cerebral peduncles.

Dosage.—Usually each dose of the cocktail contains 25 mg. of chlorpromazine, 25 mg. of promezathine, 25 mg. of pethidine combined with levallorphan; the daily requirement of each of the first three constituents varies from 100 to 300 mg. according to the severity and progress of the case. In certain circumstances the dosage of one of the constituent drugs has been altered—e.g., if the patient is reacting to slight external stimuli by violent tonic fits, it would be reasonable to increase the dosage of pethidine and levallorphan. The cocktail is given at first by intravenous drip in urgent cases, or more usually by intermittent intramuscular injection. It is possible to produce complete flaccidity in all cases if a large enough dose is given, and it may be useful to do this initially so that the temperature can be reduced from dangerously high levels, but such doses appear to depress the respiration and may lead to hypostatic pneumonia if used continuously. It has, therefore, been our object to give a sufficient dosage greatly to reduce, but not to abolish, abnormal tone. At this level the temperature will have to be controlled physically; this is a relatively easy matter.

Complications.—The only constant complication encountered, which was definitely due to chlorpromazine, was drug rash. In the final stage of this regime almost all patients suffered hypotensive attacks lasting twelve to twenty-four hours. These were predominantly systolic falls of 20–40 mm. Hg, but 6 patients required mephentermine or noradrenaline for short spells. These attacks may have been due to the chlorpromazine, but at this stage we were using pethidine without levallorphan, and since changing over to this combination we have had no further trouble. We felt that pethidine alone produced a degree of respiratory depression which led to a fall in blood-pressure due to further anoxia of the medullary centres. Pethidine and levallorphan appear to be completely safe, and, of course, no respiratory depression is produced. Laborit et al. (1955) believe that chlorpromazine causes a shift of intracellular potassium into the cells, and a lowered serum K^+ was a fairly constant finding in the treated group, though in no case did the level fall dangerously low. No severe disturbance of respiratory rate and rhythm was noted after intravenous injection of chlorpromazine in decerebrate cases; in fact return to a more normal state was the rule, although Dobkin et al. (1954) have noted irregularity of rhythm with decreased minute volume.

Cooling

If sufficient doses of the lytic cocktail are given there is little difficulty in lowering the temperature by (1) exposure of the patient with, if necessary, an open window or door, (2) the use of wet sheets, (3) strategic placing of ice-filled rubber bags, and (4) using the more complex circulating coolers. Cooling of the injection site should be avoided, and heavy cooling devices should not be allowed to press on the chest as this reduces tidal volume.

Feeding

This should be intravenous until danger of regurgitation and aspiration is over; this period lasts usually one to four weeks. All intravenous fluids are made hypertonic in the first week by adding 50% dextrose or sucrose. After this period a stomach tube is used until the patient has recovered sufficiently to feed himself. Initially during this period a constant drip of milk and water is given, and this is followed by a once-daily tube feed yielding

2200 calories (protein 100 g, fat 100 g, carbohydrate 225 g) with the following ingredients

Whole milk	40 oz
Eggs	2
Full cream dried milk	3 oz
Soya flour	2 oz
Glucose	4 oz
Salt	gr 2 5
Ferrous sulphate	gr 3
Aneurine hydrochloride	5 mg
Riboflavine	2 mg
Nicotinamide	20 mg
Pyridoxine	2 mg
Calcium	3 mg
Ascorbic acid	200 mg
Vitamin A	4500 I U
Vitamin D	1000 I U

Once the patient's tracheotomy is closed he is given small doses of water by mouth, increasing to milk-and-water mixture and then to a high-protein and high-vitamin diet

Oral feeding is most dangerous because of the incoordination of swallowing mechanisms, and if the patient is encouraged to swallow too soon aspiration into the trachea often ensues

Electrolytes

These should be estimated daily at first, particular attention being paid to serum-potassium A reduction of potassium has been a constant finding, and within twenty-four hours it falls to 8–14 mg With reference to the blood picture 10 out of 16 adults who lived long enough developed anæmia with 10 g Hb per 100 ml or less Hæmoglobin was estimated frequently and, when necessary, blood was transfused

Antibiotics

The bronchial secretion should be repeatedly examined bacteriologically as a guide to the choice of antibiotics Penicillin has usually proved sufficient if given in large doses (1 million units intramuscularly four-hourly) Tetracycline appeared to be very dangerous in 3 cases In the treated group 4 patients who received tetracycline developed profuse and persistent diarrhœa, all had received large doses of vitamins and in no case were pathogenic organisms isolated from the stool 3 of these patients became considerably dehydrated and showed a severe increase in the blood-urea We are of the opinion that, if possible, use of tetracycline should be avoided

Hypertonic Plasma

Intravenous hypertonic fluids cause a fall in the cerebrospinal-fluid pressure, and there is clinical evidence that they can improve the condition of patients with raised supratentorial pressure Hughes et al (1938) introduced hypertonic plasma in an attempt to produce a more sustained effect than that produced by non-colloidal substances and to avoid the rebound to higher pressures They claimed that a sustained fall of pressure can be produced in man, and this was confirmed in animal experiments by Bond et al (1938) We have departed from this method only by giving much larger quantities of plasma solids, 400 ml of sterile water being mixed with dried plasma of 3 pints

The uses of hypertonic plasma are (1) to prevent cerebral œdema, (2) to treat surgical shock, and (3) to reverse coning Pupils which had become fixed and dilated have become normal in size and reaction within fifteen minutes of a drip being started, with a corresponding improvement in respiration and pulse-rate

Concentrated plasma has been used in fatal cases, and at necropsy the brain has appeared much less swollen than in our previous cases where intense dehydration has been brought about by means of restricted fluid intake and mercurial diuretics No serum jaundice or other toxic effects attributable to plasma have been observed In vitro, human red blood-cells incubated in triple-strength plasma at 37°C for an hour showed no hæmolysis or other damage

Results

The control series was collected in retrospect from case-records The dangers of this procedure are appreciated, but some standard for comparison is desirable, and it is difficult to withhold treatment which appears to benefit the patient for academic reasons, however sound

All head injuries admitted under the care of two of us (I N M and L P L) between Jan 1, 1955, and Dec 11, 1956, were reviewed using the same diagnostic criteria as in the treated group—i e, partial or complete decerebrate rigidity with tonic fits and a rising temperature Of 1092 case-records considered, 56 fulfilled the criteria of selection and form the control group The treated group of 26 patients was drawn from a total of 413 consecutive admissions The difference in incidence in the two groups is not significant, so the figures can be pooled for a better estimate, giving for the syndrome an incidence of 5 5% of all head injuries

As a further check on sampling, the incidence of severe associated injuries (other than to the head) was compared in the two groups Such injuries occurred in 10 of the 26 patients in the treated group (38%) and in 16 of the 56 patients in the control group (28%) this difference is not significant ($\chi^2 = 0\ 55$ with 1 df), suggesting that the groups were comparable with respect to the violence of injury Clinical signs other than those used for selections were generally similar in the two groups, but there was a considerable difference in age distribution, the control series containing 19 more children and 3 patients over 61 years To get around this difficulty a "standardised" control group was constructed by applying the death-rates partitioned by age and sex in the crude control group to a hypothetical population with the same age and sex distribution as the treated group

Mortality

Table I shows the mortality in the control and treated groups (see also fig 3)

TABLE I—MORTALITY IN CONTROL AND TREATED GROUPS

Group	Died	Recovered	Total	Mortality (%)
Crude control	39	17	56	69 6
Standardised control	20	6	26	76 8
Treated	10	16	26	38·4

χ^2 between crude control and treated group = 4 7 with 1df
χ^2 between standardised control and treated group = 6·4 with 1df

Mortality in the treated group was 38 4%, in the crude control group (which contained a high proportion of children) 69 6%, and in the standardised control group 76 8% The difference between the mortality-rates in the treated and standardised control group is statistically significant ($\chi^2 = 6\ 4$)

Because of the diversity of type of associated injury and consequently small numbers of each type recorded, detailed comparison of effects has not been attempted However, of those 18 patients in the control group who had no severe associated injury, 6 died, compared with 4 deaths in the 8 who had severe associated injury

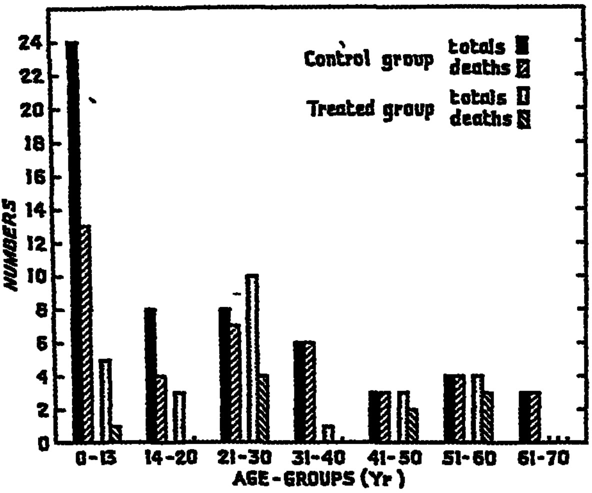

Fig 3—Mortality in control and treated groups

Survival-times

The survival-times of patients who died in the treated and control groups are shown in fig 4 and in table II

TABLE II—SURVIVAL-TIMES MEDIAN TEST

—	Control	Treated	Total
Above median	16	8	24
Below median	23	2	25
Total	39	10	49

$\chi^2 = 3{\cdot}4$ with 1 d.f. (i.e., falls just short of 5% level at 3·8)

Those in the treated group survived longer than those in the control, and by the median test this difference is found to fall just short of significance at the 5% level

The degree of residual disability in those who recovered was assessed during inpatient treatment and at follow-up clinics Of 56 patients in the control group, 17 survived 10 made a good enough recovery to pass as normal, 1 showed a personality change which made him "difficult to manage", 3 were left with a hemiparesis, and 2 of these had, in addition, homonymous hemianopia and a severe speech defect. The 3 worst results were in patients described in follow-up notes as "completely paralysed", "paraplegic, blind, and totally aphasic", and "a complete vegetable" These observations were made at one to two years after injury, when some of the patients were still improving slowly

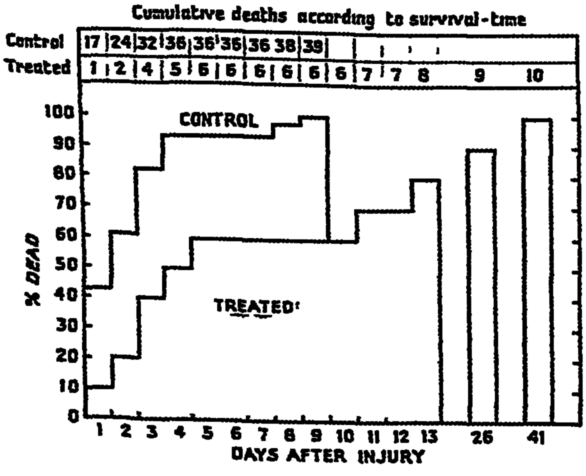

Fig 4—Survival-times in patients who died.

In the treated series, 16 patients recovered out of a total of 26

Follow-up of Patients in the Treated Group

All of the surviving patients in this group are under constant observation and have been submitted to psychological testing at regular intervals

Mental state—2 women have shown fairly pronounced mental changes for some time

One of these, a young married woman of 21, had an intellectual function below average, and there was difficulty in assessing her premorbid intelligence up to February of this year Since then, however, she has made remarkable progress and is now running her own house, and doing her own cooking and shopping, and her memory improves steadily

The other woman, a girl of 19, was very confused and violent for some time Her weight has increased enormously and she is walking well She is unable to read, and mentally, at first sight, she will pass for normal, but under close questioning it is obvious that she is slow in understanding, and we are of the opinion that there is a real deterioration in her intellect, though according to her mother (who has always proved a reliable witness) the girl is improving rapidly

1 man is somewhat euphoric and a little childish but is extremely good-tempered and works well

Physical defects—Relatively few have any physical or neurological deficit apart from the cases mentioned One man is left with definite right facial weakness, and has slight difficulty in eating and speaking because of contracture of his facial muscles He has also lost his sense of smell completely Another man is left, so far, with a permanent 3rd-nerve palsy One woman has a moderate residual left hemiplegia, which is steadily improving, and she is managing well One man has shown a fair amount of irritability and poor memory for recent and past events and has slight weakness of the left leg He also complains of dizziness

Return to work—5 patients have not yet returned to work At present 2 of these are considered fit for light work but have not yet returned 1 is likely to be fit for light work in a month and another in three months 2 patients have returned to light work, and both should return to their normal employment within a reasonable time. 9 patients have returned to their pre-accident occupation and are managing well Important factors influencing prognosis are the age and sex of the patient Children have the lowest mortality and make the best recoveries, this may be because they are less prone to respiratory insufficiency Women also seem better able to survive severe head injuries than men, the survival-rate being 5 out of 9 in the control series and 6 out of 6 in the treated series The injuries in these cases were comparable in severity to those in the men.

Conclusions and Summary

After a severe head injury, decerebrate rigidity and hyperpyrexia, either separately or together, must be regarded as an ominous development A retrospective survey showed that in this type of case the mortality was 77%

Respiratory insufficiency has been treated by immediate tracheotomy and aseptic tracheobronchial toilet, and rigidity and hyperthermia by the use of the lytic cocktail and cooling Cerebral œdema has been prevented or relieved by infusion of hypertonic plasma

The mortality has been reduced to 38·4%, and this difference has been shown to be statistically significant.

With further improvements in technique the mortality could possibly be lowered to 20%, but this will not be achieved unless it is realised that respiratory insufficiency exists from the time of the accident, and steps are immediately taken to counteract it, both during transportation to a hospital or head-injury centre and on arrival at a casualty department

It is likely that in the treated group a high proportion of patients would have died if these recent methods of treatment had not been adopted With the regime described, the majority of patients who recovered have developed little in the way of intellectual deterioration or severe mental symptoms Most of the patients will be fit to return to productive work and will not remain a burden on their family or the community

Our thanks are due to Mr I J C Frew, consultant ear, nose, and throat surgeon, Newcastle General Hospital, for his assistance in our cases and for performing all the tracheotomies at any hour of the day or night, and to Dr J G Matheson and Dr J D Whitby, consultant anæsthetists, Regional Neurosurgical Unit, Newcastle General Hospital, for the interest they have shown and for their considerable assistance But for the magnificent nursing these results could not have possibly been obtained We should like to thank our ward sisters—*Miss W Gault, Miss E Brooks*, and *Miss I Shearer*—for all their help, and the following staff nurses *Miss M Laidlaw, Miss B Brown*, and *Miss D J Jerdan*, who constantly attended our patients This type of treatment puts considerable strain on all the staff concerned, and our thanks are also due to our theatre sisters—*Miss E Hetherington, Miss M White*, and *Miss V Marley*—who have helped us in no uncertain fashion Our thanks are due to Dr S G Owen and Mr Hubert Campbell, who gave helpful advice on the analysis of the results

REFERENCES

Azambuja, N F, Lindgren, E, Sjogren, S E (1956) *Acta radiol, Stockh* 46, 215

Bond, D, Wright, D, Hughes, J (1938) *Arch Neurol Psychiat* 39, 1288

Davies, C E, McKinnon, G (1949) *Lancet*, ii, 883

Denny Brown, D, Ritchie Russell, W R (1941) *Brain*, 64, 93, 223

Dobkin, A B, Gilbert, R G B, Lamoureaux, L (1954) *Anæsthesia*, 9, 157

Greenfield, J G (1938) *Proc R Soc Med* 32, 43

Hughes, G, Mudd, S, Strecker, E A (1938) *Arch Neurol Psychiat* 99, 1276

Jefferson, G (1921) *Brit med J* ii, 683

— (1944) *ibid* i, 1

Johnson, R T (1957) *in* Modern Trends in Neurology, 2nd Series, p 274

Kinnier Wilson, S A (1920) *Brain*, 43, 220

Laborit, H, Favre, R, Guittard, R, Laborit, G (1955) *Pr méd* 63, 223

Maciver, I N, Smith, J B, Tomlinson, B E, Whitby, J D (1956) *Brit J Surg* 43, 505

— Frew, I J C, Matheson, J G (1958) *Lancet*, i, 390

Meyer, A (1920) *Arch Neurol Psychiat* 4, 387

Pocidalo, J J, Tardieu, C (1954) *C R Soc Biol, Paris*, 148, 452

Vincent, C, Thiebaut, F, Rappoport, F (1936) *Rev Neurol* 65, 536

White, J C, Brook, J R., Goldthwaite, J C, Adams, R D (1943) *Ann Surg* 118, 619

— Verlot, M, Selverstone, B, Beecher, H K (1942) *Arch Surg* 44, 1

COLOUR INDEX IN NORMAL SUBJECTS

AS DETERMINED WITH THE AID OF AN AUTOMATIC RED-CELL COUNTER

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THE construction, calibration, and performance of an automatic red-cell counter have been described elsewhere (Macfarlane, Payne, Poole, Tomlinson, and Wolff 1958) The object of constructing such a machine was to make accurate and precise red-cell counts a practical possibility in a routine hæmatological laboratory The main purpose of such counts is to make accurate estimates of the amount of hæmoglobin per cell In severe cases of iron deficiency or megaloblastic anæmias this ratio (which can be expressed either as the colour index or as the mean corpuscular hæmoglobin) shows large deviations from the normal value, but because of the great errors of visual red-cell counting (and, until comparatively recently), of hæmoglobinometry) little is known about the variation in the colour index among normal human subjects Such information is required before one can assess the significance of small changes in the colour index, now detectable for the first time

THE COLOUR INDEX OF 24 NORMAL SUBJECTS

Red-cell count (millions of red blood-cells per c mm)	Hæmoglobin (percentage of B S I standard)	Colour index
4 96	99	1 00
4 90	97	0 99
5 58	108	0 96
5 21	106	1 02
4 86	98	1 01
5 05	100	0 99
5 01	102	1 02
4 81	95	0 99
4 46	86	0 97
4 82	99	1 03
4 94	103	1 04
4 96	100	1·01
5 24	100	0 95
5 36	98	0 91
4 85	98	1 01
5 84	107	0 91
5 24	97	0 92
5 17	93	0 90
4 67	88	0 95
5 16	97	0 94
5 01	103	1 03
4 66	97	1 04
4 55	95	1·04

The results of colour-index determinations in 24 normal subjects are here reported

Investigations

Methods—Blood obtained by venepuncture was run directly into glass bottles containing Wintrobe's oxalate mixture in dry form, and mixed well Red-cell counts were made with the apparatus described by Macfarlane et al (1958) and hæmoglobin estimations with an M R C photometer (King et al 1948) The actual photometer used was one in use in the routine hæmatology laboratory of the Radcliffe Infirmary Its calibration is checked frequently and its accuracy can be relied upon

The subjects were adults of either sex Because of the small variation in the results for the whole series there was no advantage in classifying them in any way

Results—The table shows the red-cell counts, hæmoglobin levels, and colour-index values Red-cell counts are expressed as the number of cells per c mm of blood and hæmoglobin levels as percentages of the B S I Haldane hæmoglobin colour standard (B S 1079 1942, see Donaldson, Harding, and Wright 1943) The colour index has been computed in the usual way as the ratio of the hæmoglobin percentage to the red-cell count expressed as a percentage of 5 million cells per c mm The mean colour index is 0 99 and the coefficient of variation for the series is 4 93% The standard error of the mean is 0 0099 The mean value of 0 99 has 95% confidence limits of ±2%

The variation from subject to subject is obviously very small If the error of the mechanical red-cell count contributes a coefficient of variation of 2 5% and that of hæmoglobin estimation 1 6% (Macfarlane et al 1958, Biggs and Allington 1951), the coefficient of variation for a series of colour-index measurements would be expected to be at least 3% if there were no sampling error and no variation from one subject to another As the figure actually found in this series was 4 9% it can be concluded that the variation from subject to subject is so small that, even with the precise instruments now available, it cannot be estimated with any useful degree of exactitude

Discussion

The fact that the mean colour index for normal human subjects turns out to be very close to unity, when determined by the methods described above, is a fortunate coincidence. There is no theoretical reason why it should. We can now infer that the B.S.I. hæmoglobin standard corresponds closely to the hæmoglobin content of blood containing 5 million normal red cells per c.mm. It was not intended to do so when it was set up. Donaldson et al. (1943) aimed at reproducing the colour of Haldane's original carboxyhæmoglobin standard (Haldane and Smith 1900, Haldane 1901). Haldane had prepared a standard supposed to represent the mean level for healthy males. There is no reason to suppose that Haldane failed in his object, but there is reason to doubt whether Donaldson et al. reproduced the colour of Haldane's original standard. Be that as it may, the B.S.I. standard is now known to be about 7% below the mean level for healthy males (King et al. 1944) and must be regarded as arbitrary. If the mean normal colour index had turned out to be much below or above unity the question would have arisen as to whether it might be expedient to redefine 100% of hæmoglobin. Fortunately no such redefinition is either necessary or desirable.

Some clinical pathologists prefer to express the ratio of the hæmoglobin content of blood to its red-cell count as a weight of hæmoglobin per cell (the "mean corpuscular hæmoglobin") rather than as the colour index. No additional information is supplied in this way, since the mean corpuscular hæmoglobin is in effect derived from the colour index by multiplying by a constant. This constant involves a conventional figure for the hæmoglobin equivalent of the B.S.I. standard. As has been argued elsewhere (Poole 1954) the conventional figure at present generally employed is almost certainly inaccurate. Moreover, if a result is reported as the mean corpuscular hæmoglobin, the recipient of the report must know what the normal figure is before he can interpret the significance of any particular figure which may be given. In other words, he must mentally convert the mean corpuscular hæmoglobin into the colour index, a step which could have been avoided by reporting the colour index directly.

Notwithstanding these considerations, the decision as to whether to report results as the colour index or the mean corpuscular hæmoglobin must in practice be dictated by local preferences. In the series reported above the mean value for the mean corpuscular hæmoglobin is 29·4 micromicrogrammes if the hæmoglobin equivalent of the B.S.I. standard is taken as 14·8 g. per 100 ml. of blood, or 28·9 µµg. if the equivalent is taken as 14·5 g. (Poole, 1954). This is very close to the figure of 29·0 µµg. given by Wintrobe (1934), which was the mean of 698 determinations on adults of either sex and which he still regards as the best available estimate (Wintrobe 1956).

The constancy of the colour index in different normal human subjects is striking. Because of the errors of the visual red-cell count, previous information on the variation between different normal subjects is of little value. Indeed Biggs and MacMillan (1948) in a series of replicate counts on the same blood sample, found approximately twice the range that has been found here with 24 different subjects. Because of the small range of normal colour-index figures, there is every reason to hope that small deviations from the normal which can now be detected reliably, will prove significant indications of disease.

Summary

The colour index has been measured in 24 normal human subjects using an automatic red-cell counter and an M.R.C. photometer. The mean value for the series was 0·99 and the overall coefficient of variation was 4·93%.

I thank Sir Howard Florey, F.R.S., for his continued interest in this work, Dr. R. G. Macfarlane, F.R.S., in whose department most of this work was carried out, and Dr. A. H. Tomlinson for much helpful advice and criticism, and Mr. M. J. Allington, F.I.M.L.T., and other members of the staff of the routine hæmatology laboratory of the Radcliffe Infirmary, who collected the blood samples.

REFERENCES

Biggs, R., Allington, M. J. (1951) *J. clin. Path.* 4, 211.
— MacMillan, R. L. (1948) *ibid*, 1, 269.
Donaldson, R., Harding, H. G. W., Wright, G. P. (1943) *J. Path. Bact.* 55, 205.
Haldane, J. (1901) *J. Physiol.* 26, 497.
— Smith, J. L. (1900) *ibid*. 25, 331.
King, E. J., Gilchrist, M., Matheson, A. (1944) *Brit. med. J.* i, 250.
— Wootton, I. D. P., Donaldson, R., Sisson, R. B., Macfarlane, R. G. (1948) *Lancet*, ii, 971.
Macfarlane, R. G., Payne, A. M.-M., Poole, J. C. F., Tomlinson, A. H., Wolff, H. S. (1958) *Brit. J. Hæmat.* (In the press.)
Poole, J. C. F. (1954) *Lancet*, ii, 116.
Wintrobe, M. M. (1934) *Arch. intern. Med.* 54, 256.
— (1956) Clinical Hematology, p. 107. London.

PARALYTIC BONE LENGTHENING FOLLOWING POLIOMYELITIS

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POLIOMYELITIS in early years is nearly always followed by disturbance of growth of the affected extremity. The extent of this disturbance, and its associations with muscle paralysis, have been described by Stinchfield et al. (1949), Gullickson et al. (1950), and Ring (1957), who have noted the progressive discrepancy which develops between the two limbs in patients with asymmetrical residual paralysis. The attention of most investigators has been directed towards the shortening which occurs as the child grows, and the early growth of the limbs after paralysis has rarely been studied.

In the course of clinical examination of patients who had contracted poliomyelitis some time previously, our attention was drawn to children in whom lengthening of the more paralysed limb apparently developed, and radiographic studies confirmed that this did in fact occasionally occur. Whether this was a normal feature of limb paralysis was more difficult to determine, although Green and Anderson (1955) have suggested that lengthening may occur in the first year. In examining scanograms of 30 children taken during the first two years of paralysis, Lenque (1956) observed that in 12 the affected limb showed lengthening.

This phenomenon of early lengthening is rarely appreciated, partly because it is slight, partly because it is transient, and partly because the patients are often not ambulant. It is rarely of clinical significance, although occasionally raising the shoe of the unaffected leg may be necessary to maintain a level pelvis and a facile mode of walking.

Material and Method

We have confined our observations to children aged 2–12 years under the care of a single physician at Queen Mary's

Hospital for Children, Carshalton In each case the date of onset (in 1955–57) was known precisely At an initial survey those with little or no lower limb paralysis, whose stay in hospital might be expected to be very brief, were excluded It was our intention to examine and radiograph patients during the first month after onset, and thereafter at three-monthly intervals in the first year and at six-monthly intervals in the second year, a final examination being made two years after onset In fact complete records for the two years could not be obtained, and the conclusions are derived from those patients who were under our observation for six months or more

At each examination the power of the main muscle-groups of the legs was estimated and charted according to the M R C scale, where 0 represents complete paralysis and 5 represents full muscle power The muscles were examined in twenty groups and the total muscle power of the limb was expressed as the muscle score, that of the normal limb being 100 In most patients there was detectable weakness of both legs, and subtraction of the muscle score of the weaker leg from that of the stronger was used to give an index of the difference of muscle power between the limbs The lengths of the legs was measured clinically from the anterior superior spine to the medial malleolus The mid-thigh circumference and the circumference of each calf was measured, and from these measurements the amount of wasting of both thigh and calf was estimated A scanogram of the legs was then taken, and the lengths of each femur and tibia were measured upon the dry film The femur was measured from the top of the head to the intercondylar notch and the tibia from the intercondylar notch of the femur to the upper surface of the talus These measurements were made by one of us without prior knowledge of the extent of the paralysis

Observations

Of the 59 patients with a significant residual lower-limb paralysis there were 11 in whom we could detect no difference between the amount of muscle loss, or between the muscle scores, and these patients have been excluded from this series There were 48 patients with an asymmetrical lower-limb paralysis, but only 2 of these had no detectable involvement of one leg Whilst it is an advantage to have one normal leg as a standard for comparison, it is our impression that strictly unilateral involvement in the early stages of poliomyelitis is relatively rare

There were 113 clinical and X-ray examinations carried out in the 48 patients with asymmetrical paralysis of the limbs For each of the periods after onset a histogram was constructed showing the number of patients in whom the bones of the legs were equal in length and the numbers showing either shortening or lengthening of the more paralysed limb The measurements for the femur and tibia were considered separately, and any detectabl difference between the bone lengths was considered to be of significance It is difficult to define the experimental error of the scanogram, but by expressing the results in this way we hoped that errors of technique and measurement would be scattered evenly between the two limbs

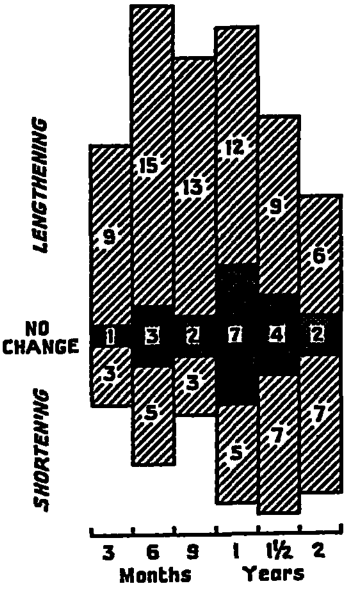

Fig 1—Histogram indicating numbers of patients with tibial lengthening or shortening in the more paralysed leg at varying periods after the onset of the disease

Excluding those in whom the limbs were of equal length, and assuming that inequality of leg length is normally distributed at random, then for the first year after onset $\chi^2=11\ 5$, P−0·02

The measurements of the tibia are shown in fig 1 Three months after onset most of the radiographs showed lengthening of the more paralysed leg, and this change was more distinct in the observations taken at six months and at nine months after onset At the end of the first year, while many of the tibiæ showed lengthening, a considerable number were shorter and the later observations indicated that shortening became progressively more common Grouping together the observations for the first year, 49 radiographs showed paralytic lengthening of the tibia, 16 showed shortening, and 13 showed equality

Observations on the femur for the same period are seen in fig 2 During the first year 38 radiographs showed paralytic lengthening of this bone, 13 showed shortening, and in 27 the bone lengths were equal In the femur, as in the tibia, during the second year shortening became the more common phenomenon In most patients the difference in length between the two bones was slight, and the maximum lengthening of the leg as a whole in this series was 11 mm comprising 3 mm in the tibia and 8 mm in the femur

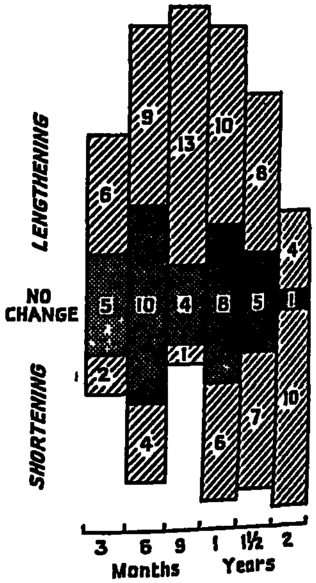

Fig 2—Histogram indicating, as in Fig 1, lengthening or shortening of the femur

For the first year $\chi^2=7\ 65$, P−0 10

The measurements of the patients with asymmetrical leg paralysis have also been examined, to determine the frequency of overall lengthening of the more paralysed limb There were 33 patients for whom there were radiographs taken in the first year after onset Of these, 23 had paralytic lengthening, in 4 cases the legs remained equal in length, and in 6 the legs became progressively shorter We were unable to separate the first from the third of these groups by simple clinical examination There was no difference between the pattern of muscle paralysis in the two groups, nor was there any clinical evidence that a vascular factor distinguished one, the paralysed limb which is longer than its fellow may still be cold and show evidence of cutaneous vascular insufficiency

Discussion

Paralytic lengthening of a limb in the first year after an attack of poliomyelitis occurs in most patients in whom there is a detectable difference between the residual muscle power of the two legs It is a temporary phase, which is almost always followed by shortening Since there is no evidence that the virus of poliomyelitis affects the bone itself, the changes in length must be secondary either to the disturbance of nerve-cells, to the paralysis of muscles, or to changes in the blood-flow of the limb

Damage to nerve cells in poliomyelitis affects primarily the anterior-horn cells, and the motor fibres from these cells have no direct spread to bone The main innervation of this tissue is derived from the autonomic nervous system, and fibres pass in along the vascular channels (Hurrell 1937) In growing bone the osteoblasts themselves may receive a nerve-supply (de Castro 1929) Damage to the sympathetic outflow may produce hyperæmia of bone, as Fell (1949) has shown by experiments in the kitten This hyperæmia may be associated with an increase in the rate of growth (Goetz et al 1955) The rate of growth may also increase after sympathectomy in the child (Harris and McDonald 1936) There is no clinical evidence that sympathetic paralysis of this type occurs in the early stages of poliomyelitis, although the distribution of the lesions would suggest this as a possible factor.

Since it has been shown that the extent of paralysis is an important factor in the disturbances of bone growth which follow poliomyelitis, it is possible that paralytic lengthening may itself be a mechanical change Paralysis of muscles is normally followed rapidly by bone atrophy (Abramson 1948), and there is commonly an inverse relationship between the rate of growth of bone in width and in length In this relationship, however, it is the epiphyseal cartilage that seems to play the dominant role, and it is unlikely that bone atrophy itself could directly influence the rate of growth in length

As a result of the muscle paralysis, changes in blood-flow in the limb undoubtedly occur and the diminution of metabolic demands by the muscle leaves available for the bone a rather greater proportion of the normal blood-supply Thus an internal shunt leading to hyperæmia of the long bones may play a part

Of the possible explanations of paralytic lengthening of bone in the early stages of poliomyelitis, one of the likeliest is that growth in breadth is indirectly associated with growth in length If we are to regard the action of the epiphyseal cartilage as twofold—(1) to add to the growth in length of bone by endochondral ossification, and (2) to add to the width of the cartilage plate by peripheral accretion—then the depression of the latter activity as a result of muscle paralysis may leave available a considerable growth potential The resulting increase in length reaches an equilibrium after a year or so as the cartilage responds to its new environment

Postscript

In describing the lengthening of bones soon after a limb has been paralysed we had the impression that this had only recently been noted We were therefore somewhat chastened to find that Ollier in 1867 also remarked on the same phenomenon

> "Le léger degré d allongement du membre que nous signalons ici n'est pas constant, probablement parce que les troubles de nutrition commencent immédiatement, mais nous l'avons observé une fois chez l homme et très fréquement chez les animaux sur lesquels nous avons expérimenté et dont nous citerons bientôt les observations On constate, dans ces cas-là, une plus grande longueur de l'os, mais un arrêt de développement en épaisseur, l'os s'est allongé en restant plus mince C'est ce que nous désignerons sous le nom d'*allongement atrophique* "

Summary

The growth of the lower limbs in the first two years after an attack of poliomyelitis has been studied in 48 children with an asymmetrical lower-limb paralysis

In the first year after the onset of the disease, of 33 patients observed, 23 showed overall lengthening of the more paralysed limb 6 patients showed progressive shortening of the limb from the onset of the disease

There appeared to be no clinical distinction between these two main groups

In the second year after onset the more paralysed limb was usually the shorter

We are greatly indebted to Dr David Lawson for permission to examine and report on patients under his care, and to Miss M M C Reardon, Miss B Laye, and Miss Stella Poole for their assistance in the organisation of this study This work was assisted by a grant from the National Fund for Poliomyelitis Research

REFERENCES

Abramson, A S (1948) *J Bone Jt Surg* 30a, 982
de Castro, F (1929) *Trab Lab Invest biol Univ Madr* 26, 215
Fell, W A (1949) *J Anat , Lond* 83, 67 Proc
Goetz, R H , du Toit, J G , Swart, B H (1955) *Acta Med scand* 152, suppl 306, p 56
Green, W T , Anderson, M (1955) *Pediat Clin N Amer* 2, 1137
Gullickson, G , Jr , Olson, M , Kottke, F J (1950) *Arch phys Med* 31, 392
Harris, R I , McDonald, J L (1936) *J Bone Jt Surg* 18, 35
Hurrell, D J (1937) *J Anat , Lond*, 72, 54
Lenque, J (1956) *J Radiol Electrol* 37, 110
Ollier, L (1867) Régenération des os, vol i, p 380 Paris
Ring, P A (1957) *Lancet*, ii, 980
Stinchfield, A J , Reidy, J A , Barr, J S (1949) *J Bone Jt Surg* 31a, 478

CHLORPROPAMIDE

A NEW HYPOGLYCÆMIC AGENT

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CARBUTAMIDE and tolbutamide have been shown to control diabetes in certain patients who would otherwise require insulin Carbutamide has been regarded by some (Kirtley 1957, Duncan and Baird 1957, Phemister 1957) as too toxic, and tolbutamide, which appears to produce fewer side-effects, has largely supplanted it Tolbutamide, however, is less potent, and because its hypoglycæmic action is of shorter duration it often has to be given thrice daily We report here results obtained in 43 cases with a new preparation, chlorpropamide [N-propyl-N-(*p*-chlorobenzene sulphonyl)urea]

The patients selected for this trial were essentially of the type described by Bertram et al (1955) as most suitable for oral therapy they were less than ten years' diabetic, were over 40 years old, and had taken insulin, if at all, for not more than two years Only 2 patients were obese, although 17 others had been so Diet alone had not sufficiently controlled the diabetes

As in our original investigation of carbutamide (Murray and Wang 1956), the dose of chlorpropamide was 1 g daily at breakfast, but no "loading" dose was given in the first two days' treatment 13 patients were in hospital and 30 were not The outpatients kept records of urine tests (using 'Clinitest') before each of the three main meals of the day This method proved reliable, corresponding well with the results of determining glucose output in twenty-four-hour collections of urine (Murray and Wang 1958) These collections were obtained in most cases on two consecutive days before starting the drug, and again on two days towards the end of a fortnight's treat-

SUMMARY OF CASES

Patients	Response to chlorpropamide	
	Success	Failure
Number treated	28 (8M, 20F)	15 (3M, 12F)
Over 40 at onset of diabetes	27 (96%)	15 (100%)
Previously obese	11 (39%)	8 (53%)
Duration of diabetes		
"New cases" (<3 months)	4	5
<10 years (excluding "new cases")	17	10
>10 years	7	0
Previously taking insulin		
For 2 years or less		
Dose <21 units	1	2
Dose >20 units	1	0
For more than 2 years		
Dose <21 units	7	2
Dose >20 units	3	1
Total	12 (43%)	5 (33%)
Previous history of ketonuria	1 (4%)	4 (27%)

ment At each attendance at the clinic, in the forenoon, the blood-sugar was estimated For the inpatients similar but more frequent observations were made

A satisfactory response to 1 g chlorpropamide daily was obtained in 28 of the 43 patients treated As the table shows, the two groups of patients—successes and failures—were similar except that ketonuria had previously been noted in 4 (27%) of the failures compared with only 1 (4%) of the successes In the successes a satisfactory response was evident generally by the second or third day, and always within seven days (mean 3 2 days), all three daily urine tests being recorded as "blue" or at worst showing an occasional "trace" (¼%) In the successful group the mean blood-sugar level fell from 273 5 mg per 100 ml before treatment to 161 8 mg at the end of two weeks, while in the unsuccessful the comparable values were 364 9 mg and 304 5 mg In these successful cases in which the urinary glucose output was determined as described above, the mean daily output was reduced from 35 5 g to 3 4 g daily, whereas the mean figures for unsuccessful cases were 58 3 g per day before chlorpropamide was given, and 59 6 g at the end of the course Since the mean blood-sugar value and the mean urinary glucose output were higher, before treatment, in the group which failed to respond, it might be supposed that this group were more severely diabetic, but no such difference was apparent clinically For example, one woman who made a rapid and excellent response to the drug had acute symptoms, ketonuria, and a blood-sugar level of 420 mg per 100 ml before treatment was started

Some of the patients had previously received carbutamide or tolbutamide Of the 28 cases responding satisfactorily to chlorpropamide, 3 had had carbutamide, 4 had had tolbutamide, and 8 had been tried with both Carbutamide 1 g daily had proved effective in all, while tolbutamide had given satisfactory results in 9 at a dose of 0 5 g three times daily, but had failed in 3, even at double this dose Among the failures with chlorpropamide 6 had been treated with the other sulphonylureas all had failed with tolbutamide but 3 had responded to carbutamide The impression gained from these few observations is that chlorpropamide is somewhat less potent than carbutamide, but definitely more potent than tolbutamide

In 5 patients who did not respond well to 1 g the dose of chlorpropamide was increased, 4 receiving 2 g daily, and the other 3 g In 3 cases this increased dosage brought satisfactory control Nevertheless these cases have been regarded as "failures", since, for reasons given below, we think it undesirable to exceed 1 g daily

Though there were no serious toxic effects, and neve any evidence of either leucopenia or thrombocytopenia, 9 patients showed side-effects—in 4 cases after the dose had been increased to 2 g The untoward effects were nausea (insufficient to call for abandonment of treatment) in 7 cases, a diffuse erythematous rash in 1, and drowsiness (unaccompanied by hypoglycæmia) in 1 Because of this evidence of toxicity, occurring particularly on highe dosage, we concluded that the dose of chlorpropamide should not exceed 1 g daily, and we are now trying smaller doses Satisfactory results have already been obtained with 0 5 g, but further experience is required before deciding on the best dosage Provisionally we would advise commencing treatment with 1 g daily, taken as a single dose, and reducing this as soon as a good response is obtained In suitable cases this method seems likely to control diabetes while avoiding undesirable side-effects

Conclusions

Chlorpropamide is an effective oral hypoglycæmic agent in the treatment of diabetes, although its action, like that of similar drugs, is somewhat unpredictable

In most cases which respond, a single daily dose of 1 gramme is sufficient, and this amount should not be exceeded If after a few days' treatment, a good response is obtained with 1 g daily, the dose should be reduced—to the lowest level found effective

We wish to thank Dr R H Gosling of Messrs Pfizer for supplies of chlorpropamide ('Diabinese'), and the staff of the biochemical department, Victoria Infirmary, Glasgow, for their willing coopera tion in this investigation

REFERENCES

Bertram, F , Benfeldt, E , Otto, H (1955) *Dtsch med Wschr* 80, 1455
Duncan, L J P , Baird, J D (1957) *Scot med J* 2, 171
Kirtley, W R (1957) *Diabetes*, 6, 72
Murray, I , Wang, I (1956) *Brit med J* ii, 452
— — (1958) *Proc 3rd Congr int Diabetes Fed*
Phemister, J C (1957) *Brit Med J* i, 199

RETENTION OF SODIUM DURING UNDERNUTRITION

WITH A NOTE ON THE RELATION OF THE EXTRACELLULAR SPACE TO GROWTH AND AGEING

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A RETENTION of water has often been described in undernutrition, and the reasons for it have been much discussed (Sinclair 1948, Keys et al 1950, McCance 1951, Helweg-Larsen et al 1952) On one point all are agreed—namely, that the excess water is retained in the extracellular space It is, however, still a question at issue whether there is an absolute increase in the amount of extracellular fluid (E C F) or whether, there being no change in the absolute amount of E C F , there is a relative increase because the cells have shrunken Precise interpretation of some workers' results is difficult because they have studied hunger œdema, but the problem of hunger œdema is not necessarily germane to that of simple undernutrition, since it may well represent a distinct pathological process Hunger œdema may affect the

TABLE I—AGES, HEIGHTS, AND INITIAL WEIGHTS OF THE EXPERIMENTAL SUBJECTS

Subject no	Sex	Age (yr)	Height (cm.)	Weight	
				kg	% of "standard weight" *
1	M	38	183	90	113
2	M	38	173	97	136
3	F	46	165	82	123

* The standard weight was calculated from the tables of the Association of Life Insurance Directors and Actuarial Society of America, New York, 1912 (Sunderman and Boerner 1949)

serous cavities (Prym 1921) and is not related to the degree of wasting (Brozek et al 1946, Helweg-Larsen et al 1952)

von Uehlinger (1947) suggested that during undernutrition the volume of the E.C.F increased to take up the space left by the loss of fat and protein tissue, and this suggestion was further developed by McCance (1951) The concept is easy to grasp in the case of the lobster, with a rigid shell and therefore a fixed volume to its body (Morgulis 1916) The same idea can without difficulty be extended to the spaces inside the bones of higher animals (Roger and Josué 1900) But, on the other hand, in these animals the elastic skin and soft connective tissues underlying it clearly must permit changes in the volume of their bodies, in fact when muscle atrophies while a limb is inside a plaster cast fluid does not take its place the limb shrinks

TABLE II—COMPOSITION OF THE EXPERIMENTAL DIETS

Subject no	Cals.	N (g)	P (mg)	K (mEq)	Na (mEq)
1	500	4 55	390	31 2	104
2	800	6 89	604	31 2	107
3	500	4 4	421	29 5	106

The calorie contents were calculated from McCance and Widdowson (1946) The chemical composition was determined by analysis.

We have made an experimental study of the gains and losses of the mineral constituents of the body-fluids during a period of undernutrition The results indicate that, although the E C F does account for a larger than normal proportion of the weight of the body in simple undernutrition, this represents a retention of what was already there rather than a gain of E.C F These findings may, we think, be explained very simply by the anatomy of the spaces which the fluid between the cells occupies The same explanation can be extended to cover the alterations in the amount of water in the tissues during growth and ageing

Material and Procedure

Three volunteers were studied Subjects 1 and 2 were male colleagues, they carried on with their normal duties during the experiments Subject 3 was a woman with osteo-arthritis of the hips, she was up during the whole of the day but was not very active All were overweight (table I) They were weighed daily under standard conditions Their experimental diets provided 500 or 800 calories, of which about a quarter was derived from protein and the remainder largely from carbohydrates (table II) Each of the experimental diets was exactly the same every day, but for one week in each experiment potassium citrate (90 mEq daily) was added. Urine was collected daily and fæces in periods of seven or eight days, and the body's gains and losses of N, P, K, and Na were measured. (The results of the balances of Cl had to be rejected because, through an oversight, the diets for analysis had been preserved with chloroform) Insensible losses were not measured Blood was taken, usually twice in each period, for the determination of the packed-cell volume (P C.V), plasma-proteins, and electrolytes The methods have been described elsewhere (Fourman 1953)

TABLE III—THE LOSSES OF WEIGHT AND THE GAINS (+) AND LOSSES (—) OF DIFFERENT ELEMENTS WITH THE EXPERIMENTAL DIETS

Subject no	Duration of experiment (days)	Loss of weight (kg)	Balances			
			N (g)	P (g)	K (mEq)	Na (mEq)
1	24	8 9	− 74 8	−7 52	−100	+153
2	42	12 9	−101 2	−8 89	−385	+287
3	24	5 9	−36·6	−5 33	−147	−36

Results

The clinical and metabolic effects of the diets we used are well known (Evans 1942, Rynearson and Gastineau 1949, Strong et al 1958) The subjects felt well during the experiments and did not become ketotic

TABLE IV—CALCULATED LOSSES OF PROTEIN TISSUE AND OF FAT

Subject no	Total weight loss (kg)	Protein loss (kg)	Fat loss (kg) (by difference)
1	8 9	2 2	6 7
2	12 9	3 0	9·9
3	5 9	1 1	4 8

Table III shows the losses of weight and also the amounts of N, P, K, and Na the subjects had lost or gained at the end of their period of undernutrition As was to be expected (Quinn et al 1954), all three subjects incurred a loss of the constituents of protein tissue, N, P, and K There was an apparent gain of Na of 6 3 mEq per day in subject 1, 7 mEq per day in subject 2, and 1 5 mEq per day in subject 3, the insensible losses account for these amounts (Freyberg and Grant 1937, Newburgh and Leaf 1950) The trend of the balances was not altered by the administration of potassium citrate (compare Duncan et al 1948) The values for the P C V and the other constituents measured in the blood did not change, and there was no evidence of hæmodilution

Discussion

From the analytical results it is possible roughly to apportion the changes in weight to different constituents of the body The balance of Na showed no significant change. This indicates there was no change in the total volume of the E C F

TABLE V—CALCULATED DAILY EXPENDITURE OF CALORIES

Subject no	from protein	from fat	from diet	Total
1	81	2300	500	2880
2	63	1890	800	2690
3	40	1600	500	2100

The losses of nitrogen were accompanied by losses of K and P It may be assumed that the loss of nitrogen represented a loss of protein tissue and not of connective tissue, for the direct analysis of rats has shown that the nitrogen lost in starvation is derived from muscle cells and not stroma (Hagan and Scow 1957)

Losses of K and P on the other hand do not depend solely on losses of protein tissue (Fenn 1939, Homburger et al 1952), and their relation to the losses of nitrogen in our experiments was quite variable We have based our calculation of the amount of protein lost on the losses of nitrogen In muscle 1 g of N corresponds to 30 g of tissue (Reifenstein et al 1945), and on this basis the losses of N corresponded to 2 2, 3 0, and 1 1 kg of tissue in subjects 1, 2, and 3 respectively The remaining loss of weight was presumably accounted for by a loss of fat (table IV)

In spite of the large contribution of protein tissue to the loss of weight in these subjects, it represented but a small gain of calories to their economy (table v) The calculated loss of fat contributed largely to the total output of calories The calculated figure for the total calorie output corresponds well with the expected calorie outputs for these subjects, and supports the interpretation placed on the results

This may be stated as a loss of cell substance and therefore of intracellular fluid—the cells shrink The total volume of E C F does not change, therefore the E C F must form a higher proportion of the total body water This interpretation agrees with the results of Moore et al 1956, and of McConkey (unpublished), obtained by measuring the E C F and the total water of the body by the dilution principle in wasted and normal people

A consideration of the spatial arrangement of the E C F explains why this must be so The E C F consists of the fluid of the plasma, the lymph, and the tissue spaces, the tissue spaces accounting for about half the whole Now the fluid of the tissue spaces is distributed as a thin film on the surface of cells, and in connective tissue (Manery 1954) Connective tissue itself is a watery gel In undernutrition the fat cells of course shrink (Jackson 1925), but there is no change in their total number The muscle cells also atrophy (Jewesbury and Topley 1913, Moulton 1920, Jackson 1925, Adams et al 1953) But all these cells must retain their surrounding film of water, and the volume of the connective tissue probably remains unchanged (Bramwell and Muir 1907, Adams et al 1953, Waterlow and Mendes 1957) Hence, as can be demonstrated by direct analysis, the water content of fat (Sedlmair 1899, Bozenraad 1911) and of muscle increases (von Voit 1866, Mendel and Rose 1912, Waterlow and Mendes 1957) The volume of the blood does *not decrease* (Perera 1946, Henschel et al 1947, Mollison 1946, Walters et al 1947, Sunderman 1947), and it is probable that the volume of lymph, which is at least as great as that of plasma (Abel et al 1938), also remains the same It is clear, then, that in undernutrition the proportion of E C F in the body must increase, though the absolute amount need not In simple undernutrition, we consider that a *relative* increase in the volume of the E C F is a geometrical necessity if each cell is to retain intact its watery environment It is unnecessary to imagine that spaces left by fat have to be filled to preserve " tissue tension "

It may be noted that the variations in E C F with age can also be interpreted on the basis of the geometrical changes in various tissues In infants the proportion of E C F is higher than in adults (Forbes et al 1956, Friis-Hansen 1957), this is largely because their muscles contain a larger proportion of water (McCance and Widdowson 1956) The muscle fibres, and the cells making them up, are smaller than in an adult, and have a larger surface area in relation to their total bulk

After the sixteenth week of embryonic life in the human the growth of muscle is by hypertrophy, and not by hyperplasia, and the total number of fibres and of cells probably does not increase (Adams et al. 1953), hence in the grown muscle the surface area of the cells is smaller in proportion to the total bulk than in infants and the amount of fluid required to bathe them is smaller in relation to the total volume of the tissue Liver on the other hand grows by hyperplasia and the size of the cells does not change appreciably It is not surprising, then, that the composition of the liver does not vary greatly with age (Nishumura and Inakake 1957)

Finally, on the basis of our interpretation, one would expect the proportion of E C F to increase in muscle when it atrophies It does (Eichelberger et al 1958) And in old age, when the fibres shrink, the water conten of muscle increases (Ranke 1865)

Summary

In three moderately obese people the effects of simple undernutrition were studied, in two of them for three weeks, in one for six weeks

They lost protein tissue and fat but they did not gain sodium There was no evidence of an increase in the absolute amount of the extracellular fluid (E C F), though the proportion of E C F in their bodies increased

It is suggested that a relative increase in the volume of the E C F must inevitably accompany wasting, if the cells which shrink are to retain their normal covering film of fluid This concept has been extended to explain the changes in the volume of the E C F which accompany growth and atrophy

This paper was written as a result of a lively discussion at a Ciba Foundation Colloquium (see Colloquia on Ageing, vol 4 Water and *Electrolyte Metabolism in relation* to Age and Sex, *pp* 113, 16 London, 1958)

A large part of the work for the experiments was done in Oxford in 1952, and we wish to express our indebtedness to Prof L J Witts and our colleagues there We are grateful to Prof Harold Scarborough for his advice and encouragement One of us (B McC) received a grant from the endowment fund of the United Cardiff Hospitals

REFERENCES

Abel, J J , Hampil, B , Jonas, A F , Chalian, W (1938) *Bull Johns Hopk Hosp* 62, 522
Adams, R D , Denny-Brown, D , Pearson, C M Diseases of Muscle London, 1953
Bozenraad, O (1911) *Dtsch Arch klin Med* 103, 120
Bramwell, B , Muir, R (1907) *Quart J Med* 1, 1
Brozek, J , Wells, S , Keys, A (1946) *Amer Rev Sov Med* 4, 70
Duncan, L E , Jr , Meyer, R J , Howard, J E (1948) *J clin Invest* 27, 359
Eichelberger, L , Roma, M , Moulder, P V (1958) *J appl Physiol* 12, 42
Evans, F A (1942) *in* Diseases of Metabolism (edited by G G Duncan), p 513 Philadelphia
Fenn, W O (1939) *J biol Chem* 128, 297
Fourman, P (1953) *Clin Sci* 11, 387
Forbes, G B , Reid, A F , Bondurant, J , Etheridge, J (1956) *Pediatrics*, 17, 334
Freyberg, R H , Grant, R L (1937) *J clin Invest* 16, 729
Friis-Hansen, B (1957) *Acta paediat , Stockh* 46, suppl 110
Hagan, S N , Scow, R O (1957) *Amer J Physiol* 188, 91
Helweg-Larsen, P , Hoffmeyer, H , Kieler, J , Thaysen, E H , Thaysen, J H , Thygesen, P , Wulff, H H (1952) *Acta med scand* 144, suppl 274
Henschel, A , Mickelsen, O , Taylor, H L , Keys, A (1947) *Amer J Physiol* 150, 170
Homburger, F , Bonner, C O , Fishman, W H (1952) *Metabolism*, 1, 435
Jackson, C M (1925) The Effects of Inanition and Malnutrition Upon Growth and Structure London
Jewesbury, R C , Topley, W W C (1913) *J Path Bact* 17, 432
Keys, A , Brozek, J , Henschel, A , Mickelsen, O , Taylor, H L (1950) *The Biology of Human Starvation Minneapolis*
McCance, R A (1951) *Spec Rep Ser med Res Coun , Lond* no 275
— Widdowson, E M (1946) The Chemical Composition of Foods *Spec Rep Ser med Res Coun , Lond* no 235
— — (1956) *Quart J exp Physiol* 41, 1
Manery, J F (1954) *Physiol Rev* 34, 334
Mendel, L B , Rose, W C (1912) *J biol Chem* 10, 255
Mollison, P L (1946) *Brit med J* i, 4
Moore, F D , McMurrey, J D , Parker, H V , Magnus, I C (1956) *Metabolism* 5, 447
Morgulis, S (1916) *J biol Chem* 24, 127
Moulton, R (1920) *ibid* 43, 67
Newburgh, L H , Leaf, A (1950) Significance of the Body Fluids in Clinical Medicine Springfield
Nishumura, H , Inakake, Y (1957) cited in *Excerpta med Amst* sect 1 (Anatomy) 12 1958
Perera, J A (1946) *J clin Invest* 25, 401
Prym, P (1921) *Münch med Wschr* 68, 74
Quinn, M , Kleeman, C R , Bass, D L , Henschel, A (1954) *Metabolism* 3, 49, 68
Ranke, J (1865) cited by C von Voit in Handbuch der Physiologie (edited by L Hermann), vol 6, pt 1, p 347 Leipzig 1881
Reifenstein, E C , Albright, F , Wells, S L (1945) *J clin Endocrin* 5 367
Roger, H , Josué (1900) *C R Soc Biol Paris*, 52, 419
Rynearson, E H , Gastineau, C F (1949) Obesity Springfield, Ill
Sedlmair, A C (1899) *Z Biol* 37, 25
Sinclair, H M (1948) *Proc R Soc Med* 41, 541
Strong, J A , Passmore R , Ritchie F J (1959) *Brit J Nutr* 12, 105
Sunderman, F W (1947) *Amer J clin Path* 17 169
— Boerner, F (1949) Normal Values in Clinical Medicine, p 633 Philadelphia
von Uehlinger E (1947) *Helv med acta*, 14, 591
von Voit C (1866) *Z Biol* 2, 307
Walters, J H , Rossiter R J Lehmann H (1947) *Lancet* i 211
Waterlow, J C , Mendes C B (1957) *Nature, Lond* 180, 1361

EXPERIMENTAL NUTRITIONAL SIDEROSIS

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ON the high incidence of severe siderosis in Africans there are now two schools of thought The first maintains that iron overload *alone* is the cause of this type of siderosis Its views are summarised by Higginson (1957)

> " The significance of diet in Bantu siderosis has yet to be established. It cannot be stated that dietary pattern (apart from excessive iron intake) is a major factor in African siderosis in this region "

On several occasions Higginson's coworkers have insisted that siderosis in Africans can be explained purely by excessive intake of iron in the food and that " no lesion of the digestive tract or any other organ need be invoked " (Walker and Arvidsson 1953)

The second school of thought, initiated by Gillman and Gillman (1945, 1951), attributes this type of siderosis primarily to an intracellular metabolic disorder, probably started by chronic malnutrition—even though the excessive bodily iron comes, of course, from the *food* Kinney, Hegsted, and Finch (1949) demonstrated that, in rats, at least, uptake of iron from an iron-rich diet varies with other components of the diet

Higginson (1957) wrote

> " In rats fed a diet of maize porridge and sour milk supplemented by iron, I was unable to demonstrate increased iron deposition as compared to a control group on a stock diet "

This was so strongly at variance with other reports (Kinney et al 1949, Finch et al 1950, Rather 1956) that we thought it essential to reinvestigate the relation of a bad diet to dietary siderosis

Experiment and Results

Adult male rats were fed either our stock ration or uncooked mealie meal, 4% ferric citrate was added to the food of half the rats on each diet These diets were fed ad libitum and fresh milk was also made freely available Liver biopsies were done on several rats in each group at 50 or 100 days, and the experiment ended at 156 days The iron contents of the diets, and also of the livers, spleens, kidneys, pancreases, blood, and entire carcasses of the rats, were determined, while iron distribution was studied histochemically in sections of the above and of several other tissues

The iron content of the whole body, and of the livers and spleens, of the groups of rats receiving the different diets is shown in the table The distribution of iron in the livers of experimental and control rats, at different stages of the experiment, is illustrated in figs 1–3

Our observations may be summarised as follows

1 The total body-iron was greater in rats on a mealie-meal diet than in rats on a good stock ration The hepatic and splenic iron were not significantly different

2 The iron uptake both from mealie-meal and from stock diets was considerably increased when iron was added to them

3 The total body-iron of rats on the iron-enriched mealie-meal diet was more than double that of rats on the iron-enriched stock diet Moreover, the hepatic iron in the former group was almost six times that in the latter On the other hand, the splenic iron in rats fed mealie meal plus iron was not quite twice that of rats fed the stock diet plus iron The table also shows that the contribution of hepatic iron to the total body-iron varied from 6 to 12% in all groups except the rats fed mealie meal plus iron In the latter, hepatic iron constituted 37% of the total body-iron, clearly indicating the predilection of the liver to siderosis, in this dietary setting The histochemical data fully substantiated these chemical findings

4 Another notable finding, not hitherto reported in experimental siderosis in rats, was that in the milder (earlier) degree

CONCENTRATION OF IRON IN LIVER, SPLEEN, AND TOTAL BODY

Diet	No of rats	Daily intake *		Concentration of iron (mg per 100 mg wet weight) in			Ratio of total liver-iron to total body-iron
		Food (g)	Iron † (mg)	Total body ‡	Liver	Spleen	
Stock	5	23	18	8 2±0 5 §	32 3±2 5	115±15 4	0 12±0 01
Stock + iron citrate	10	20	203	18 5±1 0	66 6±6 3	405±35 2	0 12±0 01
Mealie meal	5	13	0 6	12 3±0 6	22 1±2 4	114±10 3	0 06±0 02
Mealie meal + iron citrate ‖	7	11	107	45 1±2 2	367±19	765±50	0 37±0 03

* Mean daily intake per rat.
† Iron in diet and milk
‡ Iron content of perfused carcass + estimates for tissues removed for histology and chemical analysis, and for iron in plasma and hæmoglobin
§ Standard error of the mean
‖ Note greater concentrations of tissue iron despite lower daily iron intake, as compared with group on stock diet + iron citrate.

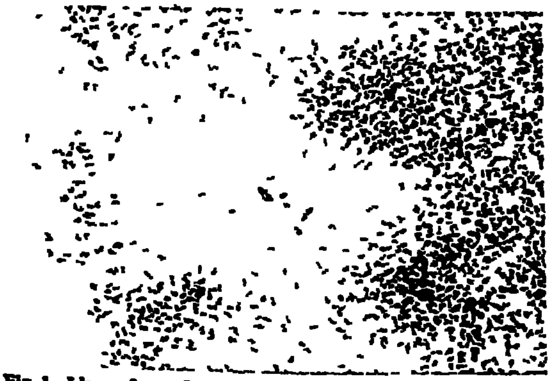

Fig 1—Liver of rat after 50 days on mealie-meal diet enriched with iron, siderosis (dark staining) of liver cells especially around portal tracts. Only a few Kupffer cells near the central vein contain iron. (× 76)

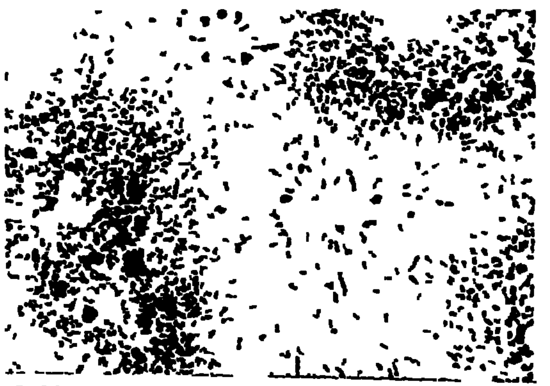

Fig 2—Liver of rat after 156 days on mealie-meal diet enriched with iron Massive siderosis with clumping of iron-containing granules in liver cells in portal half of each lobule Siderosis and clumping of siderin in sinusoidal and portal phagocytes is well marked (× 76)

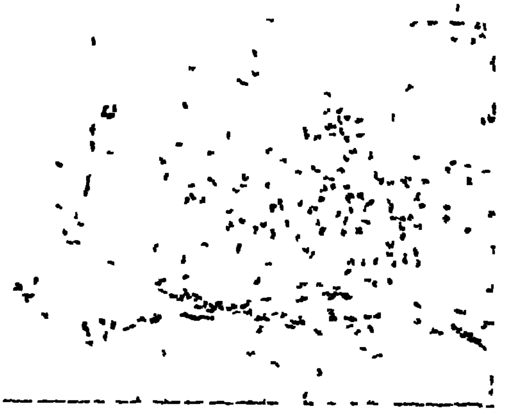

Fig 3—Liver of control rat fed good stock diet plus ferric citrate for 156 days Siderosis absent, only small amounts of iron being detectable in a few sinusoidal and portal phagocytes (× 76)

of siderosis the excess iron within the liver was at first confined to the liver cells themselves Only later, when the hepatocellular iron granules became very numerous, large, and clumped, did sinusoidal and portal phagocytes become laden with iron—possibly through ingestion of effete iron-laden liver cells This finding, in rats, exactly conforms with that noted first by Gillman and Gillman (1945, 1951) and later by Wainwright (1957) and by us (Gillman 1957, Gillman, Hathorn, and Lamont 1957, Gillman, Lamont, Hathorn, and Canham 1957), in the early stages of African siderosis

Comment

Thus, not only did the (defective) mealie-meal diet promote significant increases in the uptake of iron (especially from an iron-enriched diet), but this iron was usually detected, initially, within the liver cells It therefore seems that—as in the African, so too in rats—only when hepatic siderosis is gross may large amounts of iron be found in hepatic reticuloendothelial cells or in the epithelial and parenchymal cells of other organs—apart from spleen, bone-marrow, lymph-nodes, and intestinal mucosa

It remains to be determined whether the excessive iron uptake of rats on a bad diet is a function only of the associated unfavourable ratios of iron, calcium, or phosphate Iron uptake is known to be affected by dietary phosphate (Hegsted et al 1949) and dietary calcium (McCollum et al 1939, Chapman and Campbell 1957) The role of other dietary components such as phytate and protein (Rather 1956) also merits further study

We also want, once again, to focus attention on disturbances in intracellular metabolism as a possible basis for excessive iron uptake It has been shown for humans (Gillman, Mandelstam, and Gillman 1945, Gillman and Gillman 1951), and now (in the present study) for rats, that iron absorbed in excess from the food is initially deposited within the liver cells themselves, and not in the reticuloendothelial system In the African such hepatocellular iron deposition was shown by Gillman and Gillman (1944) to occur first in relation to mitochrondria which are now generally accepted as important foci of cell metabolism These observations are now supported by Richter's electron-microscope studies indicating that hepatocellular iron is derived from altered mitochondria or " siderosomes " (Richter 1957)

Of particular importance, in this regard, are the findings that anoxia—induced by hæmorrhage (Bothwell and Finch 1957) or decompression (Smith et al 1957, Colehour et al 1957)—increases the uptake of dietary iron, and the iron content and total iron-binding capacity of the serum The increased iron-binding capacity, so striking a phenomenon in siderotic Africans (Gillman, Lamont, Hathorn, and Canham 1957), may perhaps be one expression of seasonal nutritionally induced metabolic anoxia Moreover, these effects of anoxia are much greater in older rats than in young ones (Garcia 1957) This last finding may have as its clinical counterpart the fact that definite siderosis has not yet been observed in Africans under the age of about 14

Because of these findings, and the frequency of anoxic changes in hepatic cells in malnourished adult and infant Africans (Gillman and Gillman 1949, 1951) as well as in our experimental rats, we are now investigating the possibility that some form of cellular anoxia, induced perhaps by chronic malnutrition, may promote the prolonged excessive iron uptake, with consequent severe siderosis, so commonly found among Africans in the Union Our *preliminary findings indicate that intermittent decompression* ($1^1/_2$ hours twice weekly at about 360 mm Hg) promoted rapid and marked increases in hepatic iron, especially in rats fed the mealie meal but not the stock diet—both iron-enriched A similar but less marked trend was also noted when the calcium and phosphate contents of the two diets were equalised These findings are in line with recent evidence of the importance of intracellular iron-containing enzymes even in " iron-deficiency " states Beutler (1957) demonstrated a fall in the concentration of several of these enzymes in liver and kidney, long before anæmia was notable, he implied that the symptoms of anæmia may not be attributable solely to the decrease in oxygen-carrying powers of the blood, resulting from the low hæmoglobin, but rather to preceding and persistent derangement in intracellular iron enzymes and consequent impairment in cellular oxidation processes Even the hepatocellular iron deposits described in megaloblastic anæmias may, as suggested by Gillman and Gillman (1951, p 343) be the result of intracellular enzymic changes

Conclusion

Our present results support those of several other similar experiments in the literature showing that dietary iron overload *alone* does not readily induce severe parenchymal cell siderosis if the basal diet is good Also, a bad diet rich in iron produces much more severe siderosis than one low in iron

REFERENCES

Beutler, E (1957) *Amer J med Sci* 234, 517
Bothwell, T H, Finch, C A (1957) *Amer J digest Dis* 2, 145
Chapman, D G, Campbell, J A (1957) *Brit J Nutr* 11, 137
Colehour, J K Borsook, H, Graybiel A (1957) *Amer J Physiol* 191, 113
Finch, C A, Hegsted, M, Kinney, T D, Thomas, E D, Rath, C E,
Haskins, D, Finch, S, Fluharty, R G (1950) *Blood*, 5, 983
Garcia, J F (1957) *Amer J Physiol* 190, 19, 25, 31
Gillman, J, Gillman, T (1944) *Nature, Lond* 154, 148
— — (1945) *Arch Path* 40, 239
— — (1949) *Amer J digest Dis* 16, 348
— — (1951) Perspectives in Human Malnutrition New York
— Mandelstam, J, Gillman, T (1945) *S Afr J med Sci* 10, 109
Gillman, T (1957) Ciba Foundation Colloquia on Ageing, 3 *104*, 183
— Hathorn, M, Lamont, N McF (1957) *Lancet* ii, 146
— Lamont, N McE, Hathorn, M, Canham, P A S (1957) *ibid* p 173
Hegsted, D M, Finch, C A, Kinney, T D (1949) *J exp Med* 90, 147
Higginson, J (1957) *Lancet*, i, 994
Kinney, T D, Hegsted, D M, Finch, C A (1949) *J exp Med* 90 137
McCollum E V, Orent-Keiles, Day, H G (1939) Newer Knowledge of Nutrition p 219 New York
Rather, L J (1956) *Amer J Med* 21, 857
Richter G W (1957) *J exp Med* 106, 203, cited in *Brit med J* 1958, i 1167
Smith D L, Bierwagen, M F, Early, T K (1957) *Proc Soc exp Biol, N Y* 94, 656
Wainwright J (1957) *S Afr J lab clin Med* 3, 1
Walker, A R P, Arvidsson U B (1953) *Trans R Soc trop Med Hyg* 47, 536

ULCER UNDER THE RIBS

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IF, after a partial gastrectomy or gastrojejunal anastomosis for a peptic ulcer, the patient is unfortunate enough to develop an anastomotic ulcer, it may cause pain just above or just below the left costal margin This may lead to difficulty in diagnosis

Case-reports

Case 1—In January, 1957, a man aged 60 was referred to the thoracic department of the Bradford Royal Infirmary with recurrent peptic ulceration.

He had a duodenal perforation sutured in 1951, a partial gastrectomy in 1952, and a higher gastrectomy with Roux-en-Y reconstruction for stomal ulcer in 1955 In 1956 he developed a gastrojejunocolic fistula, and the colon and stoma were freed and each closed separately Vagotomy was attempted but abandoned After some improvement he began to deteriorate and to lose weight

The most striking feature of the history was severe attacks of intermittent pain These were localised to the left costal margin, to the præcordium, and occasionally to the left shoulder, the left arm, and the left side of the neck. The pain was so severe that he required regular doses of pethidine A barium meal in February, 1957, showed a deep ulcer penetrating the diaphragm

The patient was explored through a thoracoabdominal incision The tissues beneath the diaphragm were very œdematous, and, on separating the stomach remnant, an ulcer 5 cm in diameter was found penetrating the diaphragm and involving the chest wall The ulcer had also penetrated the spleen, and it was adherent to the transverse colon and to the jejunal loop The stomach remnant and the spleen were removed and the jejunal loop was brought up behind the transverse colon and anastomosed to the œsophagus

Postoperative recovery was satisfactory, and six months later the patient was free from pain

Case 2.—A man aged 63 was transferred to the thoracic department of the Leeds General Infirmary in September, 1956

In 1951 he had undergone a partial gastrectomy with antecolic gastrojejunostomy for a longstanding duodenal ulcer After eighteen months he developed an anastomotic ulcer which was treated medically for two years A laparotomy was then done with a view to higher partial gastrectomy, but, because of dense adhesions to the undersurface of the diaphragm, this was abandoned. A transthoracic vagotomy was performed instead

A few months later the pain returned it was severe and situated in the left hypochondrium and above the left costal margin. It was not relieved by food or by antacids A barium meal showed a huge anastomotic ulcer crater

On exploration through a left thoracoabdominal incision the omentum was seen to be adherent to the costal margin of the left diaphragm On attempting to dissect off the stomach and the anastomosis from the diaphragm a large ulcer crater was opened. It measured 5×4 cm, and it was 2 cm deep Its base involved the 6th and 7th costal cartilages and the intervening intercostal bundle A total gastrectomy was performed, together with excision of the stoma and jejunum to beyond the ulcer A Roux loop was fashioned to restore intestinal continuity Convalescence was satisfactory, and a year later the patient was free from pain and gaining weight.

Case 3—A man aged 49 had a partial gastrectomy in 1951 for an old duodenal ulcer Seven months later he began to complain of epigastric pain after meals It was situated in the left hypochondrium, and it was not relieved by food or alkalis Repeated radiological investigations were negative until June, 1954, a probable anastomotic ulcer was then demonstrated.

At *laparatomy* a stalk of fibrous tissue, 1 cm thick, was found, connecting the jejunum distal to the anastomosis to the anterior abdominal wall just below the costal margin The stalk was divided, and, after dismantling the anastomosis, the jejunum containing the ulcer was excised and an end-to-end anastomosis was carried out A higher partial gastrectomy and vagotomy were then performed

Postoperative recovery was satisfactory The man is free from pain and enjoying good health four years later

Case 4—A man aged 49 had a Bancroft partial gastrectomy in December, 1952, for a duodenal ulcer of fifteen years duration. On the seventh postoperative day he complained of stabbing pain under the left costal margin, worse on movement, it was relieved for a time by food or drink but there was severe hyperæsthesia over the affected part Treatment with local anæsthesia brought no improvement. A barium meal was reported as normal

Six months later the patient was still complaining of pain under the left costal margin, particularly when his stomach was empty, and, by January, 1954, antacids had lost their effect A barium meal at that time suggested a jejunal diverticulum only two months later did it show an ulcer crater This appeared to extend from the region of the anastomosis forwards towards the parietes

In May, 1954, a large jejunal ulcer was found at operation 5 cm. proximal to the stoma. It had perforated the diaphragm to involve the chest wall The jejunum containing the ulcer was excised, leaving the base of the ulcer behind and an end-to-end anastomosis was performed. A further partial gastrectomy and vagotomy were then done

The postoperative course was uneventful, and the patient is well and free from pain four years later

Case 5—A woman aged 48 had a cholecystectomy and a posterior gastrojejunostomy for a duodenal ulcer in 1954 In January, 1956, she began to complain of periodic pain in the epigastrium, often related to food A barium meal showed an anastomotic ulcer, and, at operation, a large ulcer was found in the efferent loop A partial gastrectomy with an antecolic gastrojejunostomy and a lesser-curve valve was carried out A week later she complained of pain in the left hypochondrium and under the left costal margin, and four days later she had a hæmatemesis of 20 oz A barium meal before discharge raised the suspicion of an anastomotic ulcer

Despite strict medical treatment the patient complained of intermittent pain under the left costal margin, in the left chest posteriorly, and in the left shoulder The pain gradually became more persistent it was aggravated by deep breathing and heat, and it was not affected by food In October, 1956, a barium meal showed a large penetrating anastomotic ulcer extending forwards

A further operation was performed through a left thoracoabdominal incision On opening the diaphragm an ulcer 3 5 cm in diameter was found in the anterior wall of the jejunum, opposite the anastomosis, it penetrated the diaphragm at its attachment to the costal margin The ulcer was dissected off the diaphragm, leaving the ulcer base behind on the chest-wall the ulcer-bearing segment of the jejunum was then removed, and a subtotal gastrectomy and vagotomy were carried out

The postoperative course was uneventful, and the patient was free from pain a year later

Discussion

Adequate partial gastrectomy results in a small gastric stump, the line of anastomosis usually lying deep to the diaphragm In such circumstances recurrent anastomotic ulceration may involve the diaphragm or occasionally the parietes just below the left costal margin In the latter event the pain becomes parietal and loses its usual relationship to eating The patient, moreover, becomes so concerned about the pain under the ribs that he tends to minimise or forget his indigestion

When the ulcer is so low that it involves the anterior abdominal wall—as used to happen when antecolic gastroenterostomies were commonly performed—there should be little difficulty in diagnosis If, however, the ulcer involves the left costal margin, either just above or just below the diaphragm, the symptoms become more difficult to interpret Pain is then referred to the left shoulder and to the back, and it is influenced by coughing, sneezing, and movement rather than by food or antacids The pain waxes and wanes as in an ordinary peptic ulcer, but some of the exacerbations are extremely severe Two of the patients needed opiates to relieve it If its cause remains undiagnosed the patients may become so disturbed as to develop bizarre symptoms thus in three of the cases neurosis was seriously *considered in the differential* diagnosis

In cases 4 and 5 the pain under the left costal margin appeared in the early postoperative period, it is debatable whether it was a symptom of an extremely early anastomotic ulcer or of a small leak Illingworth (1953) mentions the occurrence of anastomotic ulcers a few days after operation, but a small leak with local abscess-formation and subsequent fibrosis could simulate it

Summary

After an adequate partial gastrectomy the anastomosis lies deep to the left diaphragm, and an anastomotic ulcer may penetrate the diaphragm and involve the chest wall

Five cases are presented they illustrate that such ulcers are liable to cause severe parietal pain in the region of the left costal margin

The diagnosis may have to be made despite this misleading localisation and often without abnormal radiological findings

I wish to thank Mr J Davidson, Mr G H Wooler, and Mr A J C Latchmore for permission to publish these cases and for their help

REFERENCE

Illingworth, C F W (1953) Peptic Ulcer Edinburgh

LIVER BIOPSY

EXPERIENCES WITH A NEW NEEDLE

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We have recently used a liver-biopsy needle described by Menghini (1957) This preliminary communication is based on our experience of 83 biopsies

Needle

The needle, 7 cm long, is made in diameters of 1 mm, 1 5 mm, and 2 mm (fig 1)

The profile of the tip is original it has an angle of 45° at its end, and is anteriorly convex This facilitates the cutting and aspiration of the biopsy tissue

The conventional stylet or trocar is replaced by a blocking-pin towards the head of the needle, this is 2 cm long and 0 2 mm smaller in cross-section than the internal lumen of the needle The blocking-pin allows the passage of fluid to and fro but prevents the aspiration of liver tissue into the syringe and hence minimises fragmentation of the biopsy *material*

Technique

The technique is biopsy by aspiration The patient either lies supine in bed with the right side near the edge, or half-inclined on the left side The intercostal route in the mid-axillary or anterior axillary line in the right 8th or 9th intercostal space is preferred After local infiltration with 2% procaine a nick may be made in the skin with a scalpel The biopsy needle is attached to a record syringe which contains *about* 2 *ml* of *normal saline First* the *needle* is thrust into the subcutaneous tissue to an appropriate depth prefixed by an adjustable guard, and 1 ml normal saline is injected to free the needle of any subcutaneous tissue which might block its tip

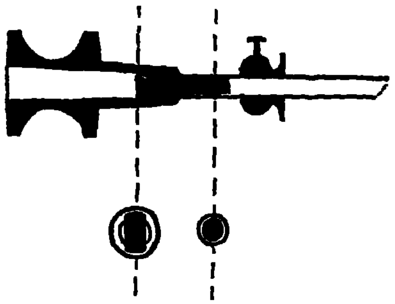

Fig 1—Liver-biopsy needle

The guard is now moved backwards 3 5–4 cm from the tip The patient holds his breath in expiration, and with constant suction at the syringe, the needle is advanced quickly into the liver It is then rapidly withdrawn

The remaining 1 ml of normal saline in the syringe helps to deliver the cylinder of liver tissue thus obtained *into* a container The puncture wound in the skin is sealed with collodion With the right elbow resting against the biopsy site to apply hæmostasis, the patient now lies on the right side for thirty minutes

Outpatients, who were admitted *for* biopsy in the morning, were fit for discharge the same evening

Liver biopsy was done where liver dysfunction needed confirmation, in unexplained hepatomegaly with normal liver-function tests, and in suspected miliary granulomatous conditions or amyloidosis The biopsy material varied from 0 5×0 1 cm to 4×0 1 cm in size it usually included a fair sample of liver tissue (fig 2) On 5 occasions the tissue was fragmented In 25 cases no *portal tracts were included in the* sections

The biopsy provided a definite diagnosis in 23 cases fatty change, and other non-specific changes were seen in 42, and normal liver tissue was obtained in 18

In a review of 20,016 hepatic biopsies from the literature Zamcheck and Sidman (1953) reported an incidence of 0 28 % of major complications Of these hæmorrhage was the most

Fig 2—Portion of liver obtained with needle (× 115)

serious it was often fatal Terry (1952) related the incidence of hæmorrhage directly to the increased bore of the needle The risks of liver biopsy have now been minimised by the reduced size of this needle and by the simplicity and speed of the technique employed Menghini, in a series of 500 biopsies with this needle, encountered no complications

In our experience so far, results of biopsy by this needle have been satisfactory There were no complications except for shoulder-tip pain in 1 case

Our thanks are due to Dr G Menghini, Institute of Clinical Medicine, University of Perugia, for demonstrating the technique and for providing us with the needles

REFERENCES

Menghini, G (1957) *Rass Fisiopat clin Terap* 7, 756
Terry, R (1952) *Brit med J* i, 1102
Zamcheck, N, Sidman, R L (1953) *New Engl J Med* 248, 1020

Preliminary Communication

SKIN TRANSPLANTATION IMMUNITY IN RELATION TO HYPERSENSITIVITY

ALTHOUGH the distinction may eventually prove to superficial, it is at present useful to divide immunolog reactions into two classes—those mediated thro orthodox humoral antibodies, and those which seem depend upon the intercession of activated blood-bo e cells To the former class belong all states of immunity that can be transferred from one animal to another serum, to the latter—a class which includes the d allergies and bacterial allergies—belong the states sensitivity that can be transferred only by lymphoid cells There is strong evidence that the reaction provoked homografts of skin (and perhaps by all other "solid homografts that make direct vascular and lymphatic connections with their hosts) is put into effect by a cellular rather than a humoral mechanism [1–7]

It is characteristic of the "cellular" immunities that they manifest themselves in the guineapig and in man as dermal hypersensitivities of the delayed type Our purpose here is to show that the reaction against skin homografts in the guineapig can likewise be made to express itself as a dermal hypersensitivity, and that the state of hypersensitivity can be transferred by activated lymphoid cells but not by serum

A typical experiment made use of two guineapigs from outbred stocks—a donor (D) and a recipient (R) Four skin homografts from D, with a total area of about 6 sq cm, were transplanted to one side of the chest of R, a position in which the regional lymph-vessels drain into the axillary nodes The pairs chosen for ordinary experimental purposes were those in which the homografts broke down in less than 12 days Two reactions could thereupon be demonstrated (*a*) the *direct reaction*, in which antigenic matter extracted from the tissues of D was injected intradermally into R, or (*b*) the *transfer reaction*, in which cells expressed from the regional lymph-nodes of R were injected intradermally into D Both reactions were marked by the development of a tuberculin-like inflammatory response with a latent period of 5–8 hours and a maximum at 24–48 hours

MATERIALS AND METHODS

The guineapigs were either outbred albinos (usually so chosen that animals D and R came from different breeders) or members of an inbred strain—the Heston strain—which has been proved by skin-grafting tests to be for all practical purposes homogeneous The technique of skin grafting has been described by Billingham and Medawar,[8] and the behaviour of skin homografts in guineapigs has been the subject of a general study by Sparrow [9,10] Guineapig R can be sensitised with tissues other than skin, but the use of skin homografts is desirable (*a*) because their donor can be kept alive, and (*b*) because they provide an outwardly visible record of the degree of immunity of the recipient, so that it is possible to eliminate or make special use of the "weak reactors" in which homografts survive for upwards of 15 days

Cell-free antigenic matter was extracted from the spleen or lymphnodes of guineapig D by the method described by Billingham, Brent, and Medawar [11]

In bare outline, cells expressed from the lymphoid tissue of the donor were washed successively in 0 15*M* NaCl, 0 05*M* NaCl, and water, and then rendered into a solution in water by exposure to ultrasonic irradiation The concentration of NaCl was restored to 0 15*M* and the precipitate of desoxyribonucleoprotein, together with miscellaneous cellular debris, removed by centrifugation for 10 min at about 2000 g The solution, now wholly free from cells or large particles, was then spun at 25,000 g for 60 min, the supernatant fluid, containing the soluble protein of the cell and other solutes, was discarded, and the sediment resuspended in Ringer-phosphate at such a concentration that the matter extracted from 1 0 g wet weight of splenic tissue was contained within 2 0 ml of the final suspension (1 0 g wet weight of splenic tissue yields about 10 mg dry weight of final sediment) The suspension is strongly opalescent and, when made from splenic tissue, has a brown or beige tinge that is a minor nuisance when interpreting weakly positive results

Antigenic substances so prepared are "complete" antigens in the sense that experiments on mice have proved them capable of giving rise to a state of sensitivity indistinguishable from that produced by an equivalent dosage of living cells administered by the intraperitoneal route

Antigenic matter was injected intradermally, in volumes of 0 1 ml, into the outer aspect of the thigh of R. The quantity injected represented the matter extracted from 50 to 5 mg initial wet weight of lymphoid tissue (i e, about 0 5 mg to 0 05 mg final dry weight)

Cellular suspensions from the "immune" regional nodes used in the transfer reaction were prepared by teasing out the nodes under about 0 5 ml Ringer-phosphate and adjusting the concentration of cells to about 100 million per ml The cells were injected in fluid volumes of 0 05 ml. and in numbers ranging from 4–6 million downwards

The results of both the direct and the transfer reactions were scored against an arbitrary scale (+ to +++++) which took account of the area of inflammation and of its intensity in terms of reddening, hardness, and swelling

RESULTS THE DIRECT REACTION

The "direct reaction" was described above as the reaction that is produced by the intradermal injection into a sensitised recipient (R) of antigenic matter extracted from the tissues of the homograft donor (D)

Thirty independent trials of the direct reaction gave positive results of variable intensity, three others were negative or marginally positive, but the recipients proved

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1 Mitchison, N A *Nature, Lond* 1953, 171, 267
2 Mitchison, N A. *Proc roy Soc* B, 1954, 142, 72
3 Billingham, R. E., Brent, L, Medawar, P B *ibid* 1954, 143, 58
4 Billingham, R. E, Brent, L, Medawar, P B *Philos Trans roy Soc* B, 1956, 239, 357
5 Burnet, F M., Fenner, F The Production of Antibodies Melbourne, 1949
6 Medawar P B In Preservation and Transplantation of Normal Tissues (Ciba Foundation Symposium), London 1954
7 Favour, C. B *Transplantation Bull* 1954, 1, 145
8 Billingham, R E., Medawar, P B *J exp Biol* 1951, 28, 385
9 Sparrow, E. M *J Endocrin* 1953, 9, 101
10 Sparrow, E. M *Ibid* 1954, 11, 57
11 Billingham, R E., Brent, L., Medawar, P B *Transplantation Bull* (in the press)

to be pregnant and must therefore be discounted * Animals which gave a +++++ response after injection of the antigen extracted from 50 mg initial wet weight of D splenic tissue still gave perceptibly positive responses (+ or ++) to the injection of one-tenth of this quantity The weakest positive response elicited by a high dose of antigen was ++ evidently there were wide variations in the degree of sensitivity of the recipients, though all had rejected their skin homografts within 12 days of transplantation Experience with mice, however, has shown that even over a wide range of antigenic dissimilarities between donor and recipient the survival-times of homografts may still fall within the range 9–12 days [14]

The histological appearance of a 24-hour reaction site—kindly interpreted for us by Dr P G H Gell—was essentially similar to that of a tuberculin reaction

Living donor cells—preferably lymphoid cells—may be used instead of cell-free extracts to elicit the direct reaction The reactions were more intensely red and compact than those elicited by cell-free extracts, but table I, based upon three *independent trials, shows that their variability from one animal* to another was just as great The intradermal injection of donor serum into sensitised recipients was ineffective

TABLE I—VARIATIONS BETWEEN THE RESULTS OF THREE TRIALS OF THE DIRECT REACTION (SEE TEXT) USING LIVING D CELLS AS SOURCE OF ANTIGEN CELL DOSAGES EXPRESSED IN MILLIONS

Experiment	Cell dose	Score	Experiment	Cell dose	Score	Experiment	Cell dose	Score
55	15	++++	57	30	+++	58	12	+++++
	5	+++		7 5	++		6	+++++
	1 6	++		3 8	±		3	+++
	0 5	+		1 9	±		2	++
	0 16	+						

The dermal hypersensitivity of four R guineapigs which had each been immunised by four D skin homografts was not strengthened by repeated weekly injections of 2 5 ml of D blood, in one animal certainly, and possibly in two, the intensity of the reaction declined This result has raised in our minds the possibility of a "desensitisation" brought about by the action of humoral antibodies Variations from one pair of guineapigs to another are to be expected, just as the ease of producing "enhancement" varies from one pair of mouse strains to another in accordance with their genetical constitution at the H-2 locus [15]

It has not been possible to demonstrate the direct reaction in the general body skin or foot pads of mice belonging to several different strains, the results with rabbits have been variable and inconclusive

As controls for the specificity of the direct reaction, high doses of cell-free antigen were injected intradermally into thirteen non-immune guineapigs, and up to 6 million normal (non-sensitised) lymphoid cells were injected into thirty-seven others Most of the injections elicited no reaction, a small minority secured a maximal score of ± These are not precise controls, for the *inflammatory* response provoked by the intradermal injection of antigen might be a non-specific consequence of the state of sensitivity as such Two exact controls took the form of sensitising an inbred (Heston) guineapig *with skin* homografts from a non-inbred donor Although in a sensitive state, the inbred recipient failed to respond to an intradermal injection of antigen extracted from the spleen of a Heston donor, that the antigen itself was active was proved by its power to elicit a strong reaction after injection into a non-inbred guineapig which had been sensitised by skin graft from a Heston donor Hence the direct reaction does no merely depend upon the existence of a state of sensitivity depends upon the existence of a state of sensitivity directe against the antigens used in the skin test

TABLE II—RANGE AND DISTRIBUTION OF SCORES OBTAINED IN THIRTE INDEPENDENT TRIALS OF THE TRANSFER REACTION REGIONAL CONTRALATERAL NODES THE NUMBERS ARE THOSE OF THE EXPER MENTAL ANIMALS

Score	Source of cells	
	Regional nodes	Contralateral nodes
5 or >5	10, 17, 23, 29, 31, 35, 59, 65, 66	10, 65, 66
4		
3	32A, 32B	
2	19	35
1		
± or 0	21	

RESULTS THE TRANSFER REACTION

The "transfer reaction" was described above as th reaction that is produced by the intradermal injectio into a homograft donor (D) of cells expressed from th regional lymph-nodes of a sensitised recipient (R)

The transfer reaction produced by the injection of 4– million sensitised lymphoid cells is stronger than th direct reaction produced by the injection of concentrated antigenic extracts it tends to reach its maximum a little later (48 hours as opposed to 36) and to last longer, to be more compact and to give rise to redder, harder, and more prominent swellings In its extreme form (scored higher than +++++) the reaction may proceed to limited central necrosis

The scores of thirteen independent trials of the transfer reaction are summarised in table II We are unable to account for the one animal from which no response of any kind was secured The evidence of Mitchison [2] and of Billingham, Brent, and Medawar [3] had led us to expect that the reactions elicited by cells taken from the *contra*lateral lymph-nodes would be very feeble In three of four trials, however (table II), they were just as strong as the reactions elicited by cells from the homolateral (regional) nodes

Among pairs of guineapigs (D and R) chosen at random it sometimes happens that homografts transplanted from D to R live longer than the usual 9 or 10 days these are the "weak reactors" referred to in the section on Methods, and they have made it possible for us to show that the ability of lymph-node cells to elicit the transfer reaction does indeed depend upon the state of sensitivity of the animal from which they were taken

TABLE III—TRANSFER REACTION SCORES OBTAINED IN THE DONORS OF "WEAKLY REACTING" PAIRS (SEE TEXT)

Experiment	Homograft survival-time D→R	Day of transfer of cells, R→D	Maximum score
24	17	17	+–
53	20–25	30	±
54	20–25	30	+
33	40–42	17	±
39	>>30	18	0

The tests summarised in table III were carried out either before or immediately *after these unusually long-lived homografts* had broken down the transfer reactions were feeble or absent

The transfer reaction in rabbits (*unlike the direct reaction*) is particularly violent and long-lasting All experiments with mice have given negative results, regardless of whether the skin at the time of injection was quiescent or *in the midst of a* cycle of hair growth

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* Pregnancy is known to prolong the survival of homografts in rabbits [12] and to subdue the inflammatory processes that accompany the breakdown of homografts in mice [13] Its effect upon transplantation immunity in guineapigs is not yet known

12 Heslop R W Krohn, P L, Sparrow, E M *J Endocrin* 1954, 10, 325
13 Medawar, P B, Sparrow, E M *ibid* 1956, 14, 240
14 Billingham R E, Brent, L, Medawar, P B, Sparrow, E M *Proc roy Soc B*, 1951, 143 43
15 Snell, G D *J nat Cancer Inst* 1954, 15, 665

It is a matter of great theoretical importance to determine whether or not the transfer reaction can be provoked by *serum* taken from sensitised recipients

Fifteen independent tests were made, including four in which the recipients had been sensitised not only by skin grafts but also by repeated weekly injections of donor blood Half produced no visible reaction, and none of the remainder secured a response greater than + The reactions produced by serum were probably non-specific, for they occurred equally often in the thirty-four trials in which normal guineapig serum was injected intradermally into normal recipients They differed in timing from even the weakest reactions brought about by the transfer of low doses of sensitised cells a feeble and diffuse inflammation was usually perceptible within 2–3 hours of injection and had faded by the 24th hour

The transfer of immune lymphoid cells which had been heated to 48 5° for 20 min produced no reaction greater than +

In three experiments the procedures of the direct and transfer reactions were combined 5–7 5 million sensitised regional lymph-node cells from a Heston inbred guineapig R were mixed with 8–10 million normal lymph-node cells (representing "antigen") from the corresponding donor D and the mixture was at once injected into a third guineapig belonging to the same inbred strain as R. The reaction elicited by the mixture was +++ in all three cases, D cells alone produced a reaction of +, and the sensitised R cells alone produced no reaction whatsoever Although the reactions produced by the mixture were unexpectedly weak, they were strong enough to justify the obvious supposition that the tuberculin-like inflammatory response which we have been studying is due to some local interaction between antigen and sensitised lymphoid cells

Controls for the specificity of the transfer reaction require special consideration In the preceding section it was said that only in a small minority of thirty-seven independent trials did the intradermal injection of normal lymphoid cells into normal animals produce a reaction as great as + To these may be added the five animals registered in table III, in which lymphoid cells were taken from animals which, though carrying homografts, were not yet sensitive, or only feebly sensitive, when the transfer tests were carried out These controls do not eliminate the possibility that the transfer reaction might represent some non-specific consequence of the state of sensitivity as such. Six experiments were therefore done in which highly sensitised cells from inbred (Heston) recipients were injected either into the recipient itself or into some other member of the Heston inbred strain The reactions were negative throughout In four of the six experiments the sensitised Heston cells were injected intradermally into the homologous donor, to assure ourselves of their ability to provoke a strong reaction.

It should be added that "controls" in which sensitised cells are injected into a third guineapig related neither to D nor R are fundamentally unsatisfactory in design The third guineapig must often possess antigens in common with D, and should therefore react with a violence proportional to the degree of antigenic overlap between them

DISCUSSION

At present we have no reason to question the obvious assumption that the "transfer reaction" does indeed represent a passive cellular transference of the state of sensitivity that is disclosed by the "direct reaction" In the direct reaction, an animal in a generalised state of sensitivity is confronted locally with antigenic matter, and in the transfer reaction an animal in which "antigen" is distributed throughout the body is confronted locally with sensitised lymphoid cells The difference between the two reactions is probably one of tactics and not of principle, both appear to depend upon a local interaction between antigens and sensitised lymphoid cells

The fact that the homograft reaction in guineapigs can be made to express itself as a dermal hypersensitivity of the tuberculin type, transferable by activated lymphoid cells but not by serum, adds strength to the analogy that has so often been drawn between the two The homograft reaction, in the form in which we have considered it, evidently belongs to the same general class of immunological reactions as the drug and bacterial allergies, the sensitivities produced by the injection of small quantities of antigen-antibody complex,[16] and that component of autoimmune reactions which is responsible for the lymphocytic infiltration and partial or complete destruction of the tissue against which the immunity is directed [17–18] All these reactions can be made to manifest themselves as dermal hypersensitivities of the delayed type, and in all of them—including the homograft reaction [2 3 19]—the "antibodies" behave as if they were attached to cells

The "second set" reaction that is so familiar to students of tissue transplantation—the accelerated athreptic breakdown of a second homograft on an animal which has already rejected a first—is probably a general manifestation of the phenomenon which in guineapigs and man takes the peculiar form of a dermal hypersensitivity The second-set reaction is analogous to a skin reaction in the sense that it shows up a pre-existing state of sensitivity, it can hardly depend upon a "secondary response" as the immunologist understands that term

Two other phenomena are almost certainly cognate with the direct form of the hypersensitivity reaction as we have described it in the text The first is the "recall flare" of Rapaport and Converse,[20] in which the otherwise quiet site of a rejected human homograft becomes swollen and red over the period during which a living homograft subsequently transplanted from the same donor is being rejected. The existence of this recall flare suggests that "homograft antigen" or some component of it still lingers in or around the site of a rejected homograft, and this in turn might account for the extraordinarily long persistence of the state of sensitivity produced by skin homografts and other solid homografts, when compared with the evanescent sensitivity produced by the intraperitoneal injection of dissociated cells (Billingham, Brent, Brown, and Medawar, unpublished work)

The second is the phenomenon first described by F K Sanders and since studied in detail by Darcy [21] Homografts killed by repeated freezing and thawing provoke no reaction on their own account, but become the seat of a brisk infiltration by round cells when they are implanted into rabbits which have been sensitised beforehand by living homografts from the same donor The dead homografts presumably contain some component of the sensitising antigens present in living homografts The antigen which we have used in analysing the direct reaction is, however, a "complete" antigen, in the sense that it has the power not merely to reveal a pre-existing state of sensitivity, but also to provoke it in the first place It has not yet been proved that this complete antigen is necessary to evoke the direct reaction some fraction of it may suffice

Our inability to secure the transfer reaction with "immune" serum tells against the view that the inflammatory changes which we have described are due to a reactivity of the Arthus type The peculiar violence of the transfer reaction in rabbits is nevertheless suspicious, and it is by no means impossible that, with hyperimmunised animals especially, some Arthus-like component should be present

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16 Uhr, J W, Salvin, S B, Pappenheimer, A M *J exp Med* 1957, 105, 11
17 Lipton, M M, Freund, J *J Immunol* 1953, 71, 98, 380
18 Freund, J, Thompson, C E, Lipton, M M *J exp Med* 1955, 101, 591
19 Berman, J H, Brent, L *Ann N Y Acad Sci* (in the press)
20 Rapaport, F, Converse, J M *Ann Surg* 1958, 147, 273
21 Darcy, D A *J Path Bact* 1955, 70, 143

SUMMARY

The reaction against skin homografts in guineapigs can be made to express itself as a hypersensitivity reaction of the delayed type

Two reactions are described (*a*) a "direct reaction", in which antigenic matter extracted from the tissues of a homograft donor is injected intradermally into a sensitised recipient, and (*b*) a "transfer reaction", in which cells taken from the regional lymph nodes of a sensitised recipient are injected intradermally into the homograft donor

The transfer reaction is thought to represent a passive cellular transference of the state of sensitivity revealed by the direct reaction The transfer reaction was not elicited by "immune" serum or by heat-killed lymphoid cells

The occurrence of these reactions strengthens the analogy between skin transplantation immunity and other immunological reactions that are thought to be mediated through cells

This work has been helped by grants from the Nuffield Foundation and the British Empire Cancer Campaign One of us (J B B) is a research scholar of the Medical Research Council

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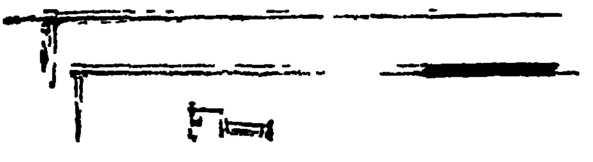
New Inventions

FLEXIBLE ŒSOPHAGOSCOPE

A few years ago the Genito-Urinary Manufacturing Company Ltd. made up for me a flexible œsophagoscope which consisted of an outer tube, the distal part being flexible, and an inner tube carrying the light and lens system, which was also flexible in its distal part

Experience has shown that this complicated and expensive flexible inner tube is not essential, and the œsophagoscope has been modified using a straight inner tube carrying the light and built-in suction and with a telescope attachment



To pass the instrument, an œsophageal tube no 30 FG (18EG 60BE) is threaded through the outer tube projecting about 8 in from the end, and this enables the œsophagoscope to be passed very easily into the œsophagus of a conscious patient who has had premedication and a local anæsthetic applied to the throat The œsophageal tube is then withdrawn and the rigid tube is inserted The telescope attachment is joined and enables an excellent view to be obtained A biopsy specimen can easily be taken using 60 cm œsophageal biopsy forceps

The apparatus is supplied by the Genito-Urinary Manufacturing Company, Ltd , of 28A, Devonshire Street, London, W 1

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F Avery Jones
M D Lond , F R.C.P

Reviews of Books

Orthopædic Disorders

Ernest Aegerter, M D , professor of pathology and director of the department of pathology, Temple University Medical Centre and School of Medicine, professor of orthopædic pathology, Philadelphia General Hospital, J A Kirkpatrick, Jr , M.D , radiologist, St Christopher's Hospital for Children and Children's Heart Hospital, assistant professor of radiology, Temple University Medical Centre Philadelphia and London W B Saunders 1958 Pp 602 87*s* 6*d*

This is one of the most original and praiseworthy orthopædic textbooks that has appeared in recent years It has been written, not by a surgeon, but jointly by a pathologist and a radiologist Together they have reviewed all the common (and many of the rare) diseases of the skeleton In the case of each they have tried to show just how the pathological changes produce the typical clinical features, and how they give rise to radiographic signs

The main body of the book is prefaced by half a dozen brief chapters on the normal histogenesis of bone and connective tissue For the sections that follow, the literature has obviously been painstakingly surveyed and abstracted In consequence even a very experienced surgeon, looking up a condition with which he is familiar, is likely to discover facts previously unknown to him Yet this is not a "heavy" volume, abounding in paragraphs of small print and lengthy footnotes What distinguishes this work is that, though its scope is wider than the modest title suggests, it is written throughout in a lucid, consistent, and elegant style

The Interference Microscope in Biological Research

A J Hale, M B , CH B , PH D , lecturer in physiology, University of Glasgow Edinburgh E & S Livingstone 1958 Pp 114 20s

The phase-contrast microscope is now widely used for studying transparent specimens such as living cells The interference microscope is newer and less familiar The images it produces are free from certain defects inherent in phase contrast, but its most important advantage is that it can be used to make quantitative measurements of optical-path difference This quantity can be related to the dry mass per unit area of a cell, so that it is now possible to "weigh" parts of cells In this book the more important instruments and the basic theory underlying their use are described It should prove useful to biological and medical workers, but its value to the uninitiated might have been increased if more indication of the types of problem which can be investigated had been given

Collected Papers

Through Pædiatrics to Psychoanalysis D W Winnicott, F R C P London Tavistock Publications 1958 Pp 350 35*s*

In accordance with the established practice of psychoanalysts, Dr Winnicott has assembled under one cover the articles he has written in various journals They extend over a period of twenty-one years and are preceded by two chapters, on anxiety and fidgetiness, from an earlier book of his on disorders of childhood Dr Winnicott's entry into the field of pædiatrics and the beginning of his personal psychoanalysis occurred in the same year, three years after he qualified Since then he has become more and more occupied with the psychoanalytical aspects of children's illnesses, and has shown himself to have a strong sense of mission This is well illustrated in the last contribution in the book—an address to the Eighth International Congress of Pædiatrics—in which he urges that all pædiatricians who wish to treat the psychological troubles of children must take a psychoanalytical training Dr Winnicott is one of the leading British psychoanalysts, his innovations in theory have attracted much attention and he has developed a notable skill in conveying his views to large sections of the public It is therefore to be regretted that, as the bibliography of this book shows, he has disregarded almost entirely the invaluable contributions to child psychology and psychiatry made by non-psychoanalysts This concentration of interest, however, enables him to present effectively his experience and views

THE LANCET

LONDON 13 SEPTEMBER 1958

The Report on Prisons

THE latest report on prisons[1] is disquieting yet in some ways encouraging. It is disquieting mainly in its revelation of still more overcrowding: the increase in prison population seems likely to engulf the institutions now in preparation and preclude the improvement expected from them. Between 1952 and 1956 the average number in prisons and borstals dropped from 22,558 to 19,776, but in the early months of this year it was, at 24,700, the highest yet recorded.

One of the notable facts given in the report is that last year the prisons received no fewer than 39,000 men who had not been sentenced. The practice of remanding in custody sometimes seems haphazard, and this high figure strengthens the suspicion that it is often unnecessary. When specialist reports on a prisoner are needed they can often be obtained as easily while he is on bail. Some magistrates seem to remand a man in prison whom they have no intention of sentencing, "to give him a taste of it"; indeed the report mentions that 38–40% of the men imprisoned before trial are not imprisoned after it. This policy may appeal to some, but it must also tend to bring justice into disrepute. Of the men actually under sentence the majority (68%) were in prison for six months or less, while for women the figure was 85%. Perhaps this short-term population could be reduced by wider use of probation (though that excellent service must already be stretched to very near its limit), or by the introduction of the suspended sentence, of which Dr SCHMIDEBERG recently spoke so enthusiastically from American experience[2], or, indeed, by increasing the use of our own conditional discharges. For the people sent to prison for a long time, parole gives an excellent incentive and could be used much more widely, as the "Bristol experiment" (placement of prisoners in hostels) has shown.

Among the reasons for imprisonment we note 5539 receptions for non-payment of fine: in 49% of cases the prisoner had *not* (report's italics) been allowed time to pay. Though the use of statistics in penology is full of hazards[3] it is at least worth mentioning that the increase in crimes of violence against the person, which has been greeted with such clamour, is in fact proportionate to the total increase (about a ninth since 1954), except in the 15–21 age-group. Sexual offences, however, show a larger increase in these imprisonment figures (of about a third), larceny remained static and fraud actually decreased. The rise in crime has hit the borstals particularly hard, and the report says that boys have waited for up to six weeks in local prisons for a place in a reception centre. But these are not the only young people in prisons: we read with some horror that 370 boys and girls between 14 and 17 were remanded there; and 1 boy aged 15, and 8 aged 16, were actually sentenced to terms of imprisonment—under the Criminal Justice Act of 1948, section 17(1).

Looking to the report for encouragement, we read of a modest increase in psychiatric services and of successes in a group-psychotherapy unit. Of great interest, too, is the related success of the "Norwich experiment", which comprises the regular evening "association" of large numbers of men with very few officers present. A group atmosphere seems to have been created, and, to quote a governor's report, "the few anti-social and intractable types were contained by this atmosphere, confirming the impression that so far as possible each group must learn to live with and tolerate all types." This remarkable governor also writes of the "identification of officers with individual inmates" which results, and of the value of such personal relationships. This is but one of a series of extracts from the annual reports of senior staff which, in appendix 1, make perhaps the most interesting reading. A new wind really does seem to be blowing through our ancient gaols, and even experienced prisoners are known to admit that things have changed for the better over the last couple of years. Recruitment of the right type of prison officer is extremely important, and the report says little about this, although it is perhaps reassuring to read that, of men approaching the authorities, only 1 in 35 is appointed, of women inquirers, 1 in 63 is chosen.

The commissioners cannot be expected, perhaps, to suggest reforms in such a volume as this, but in our view the essence of progress must be to transform the prison into a truly "therapeutic community". This endeavour will have much in common with what many mental hospitals are trying to do, and the two spheres should become more aware of each other. Such projects would draw much from the wider aspects of Dr. MAXWELL JONES' very interesting work at Belmont, and from Dr CEDRIC SIMPSON's unit at Wormwood Scrubs. Though the running of a whole prison on something approaching these lines is still a long way off, some enlightened administrations are finding their way there gradually, and they must be watched and encouraged. It really is time that the commissioners and the trade-unions came to some better understanding about contract work in prisons. Too little is done towards rehabilitation, and too many men moulder away doing nothing useful or constructive. The day is long past when we should be content to regard such misery and waste as a proper part of punishment: if the inmates of a Russian prison[4] can earn reasonable wages, which are paid to dependants, why should not ours have an equal chance of regaining usefulness and self-respect? The Russian attitude towards non-political crime is liberal, and in their prisons the internal discipline is said to be handled by a panel of prisoners who sit in judgment on their fellows. This form of group technique has not been tried here yet, though the commissioners report a "working party" of prisoners and very senior officers which discussed round a table problems of prison administration—*an event said to be without precedent*

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[1] Report of the Commissioners of Prisons for 1957. Cmd. 496. 1958. Pp 187. 9s 6d.

[2] See *Lancet*, Aug 2, 1958, p 249.

[3] *Ibid* July 12, 1958, p 79.

[4] *Illustrated*, March 1, 1958, p 24.

The fact that deficiencies in the prison service are as bad as they are, that research is so scanty, and that progress is so slow does not necessarily put the commissioners under a cloud They are but doing the best *with what they have, and if they have little it is we,* the public, that are to blame This branch of therapeutics, though very important to our society, is given low priority.

Sphincter and Hiatus

UNTIL quite recently our great protector that lies between the stomach and the gullet might well have been called the Sphinx—even the Sphinx of Sphinxes—because its behaviour seemed so enigmatic The name is more apt than it may seem, for the Sphinx of Thebes was not only a riddler but also a *sphincter* or strangler (of those who could not solve her riddles) Today the riddles of the cardiac or œsophageal sphinx are happily being solved Apart from the personal experience of each one of us that, as a rule, there is some effective check to the reflux of stomach contents into the œsophagus, we now feel more sure, from the work of FYKE et al,[1] ATKINSON et al,[2] and CREAMER and PIERCE,[3] among others, that there really is a sphincter around the lower end of the gullet, even though it has not yet been displayed by dissection There seems to be a band of higher muscular tension around the lower 2–3 cm of the œsophagus which resists the pressure gradient between abdomen and thorax It relaxes as the cup is raised to the lips in drinking, and so allows fast-moving liquid to pass through before the peristaltic wave arrives at the cardia and peters out there It also relaxes at an early stage in the simpler act of swallowing These physiological features are thought by CREAMER and PIERCE [3] to explain why certain careful investigators in the past have failed to identify the sphincter

Normally this zone of higher muscular tension lies partly in the abdomen, below the diaphragmatic hiatus (As a recording tube is withdrawn from the stomach, the position of the hiatus is indicated by a fall in pressure and by a simultaneous inversion of the respiratory waves in the tracing) Being thus in contact with the abdominal pressure, the sphincter responds when this increases As in a bucket of fluid, pressure in the abdomen is greatest at the lowest point (CANNON,[4] FYKE et al [1]), and even tilting of the body by 15° will raise the pressure around the intra-abdominal portion of the cardiac sphincter, perhaps also evoking protective contraction In people with hiatus hernia the abdominal pressures are carried into the intrathoracic part of the stomach above this, in a proportion of cases, one can detect a sphincteric zone in which pressure is increased, and above this again there is the sudden drop and inversion signifying a thoracic pattern Sometimes the sphincteric zone shows little or no increase in tension, and in these cases acid reflux readily occurs ATKINSON et al [2] have found good correlation between the clinical evidence of reflux and the graphic evidence that the sphincter is poorly developed If this finding is fully substantiated by further experience, it will explain why hiatus hernia presents in so many different ways—particularly as regards the presence or absence of acid reflux—and why patients may have reflux though they have no hernia at all The evidence of pressure tracings is the more valuable because in some cases the presence of a hiatus hernia is not revealed by radiography Moreover, pressure tracings and cinefluoroscopy in patients with hiatus hernia have also *shown* (CROSS et al [5]) *abnormal* muscular behaviour in other parts of the gullet, particularly muscular overaction in the lower part, together with underaction in the upper part Correlation of these with dysphagia will sometimes provide a satisfactory explanation for this symptom, in cases of œsophagitis, ulcer, or stricture *In the same way,* OLSEN and CREAMER [6] have elucidated the distinction between achalasia and diffuse spasm

Despite the doubts raised so cogently by Dr HOUGHTON in his letter last week,[7] we shall be surprised if the pressure tracing does not turn out to be an important means of investigating patients with hiatus hernia and other disorders of the gullet Even with a large hernia, a good sphincter (if such exists) should prevent reflux and so render surgical repair unnecessary, provided other symptoms such as pain and eructation are not serious Where there is reflux and the sphincter is poor or absent, it may at first sight seem useless to repair the hernia, for the sphincter will still be weak But if the sphincter is moved to below the diaphragm, it may be reinforced by the abdominal pressure—which explains why some cases of reflux are cured by simple surgical repair (BOTHA's [8] conception of the rosette of mucosal folds rendered active or erect by the *muscularis, as check against reflux,* is complementary, not alternative to nor exclusive of the idea of the sphincter) Mere tightening of the hiatus, even with creation of an acute angle between the lower end of the gullet and the fundus of the stomach, is of more doubtful value against reflux Again, in patients whose symptoms—particularly acid reflux—recur after surgical repair, the pressure tracing may prove to be of great value If, in a patient with troublesome reflux, the repair is found to be intact but the sphincter poor or absent, a difficult situation will be evident Perhaps some drastic measure to diminish gastric acidity, will be required, perhaps a surgical attempt should be made to fashion a check against reflux, which will nevertheless allow vomiting when necessary, or perhaps the jejunal segment of MERENDINO and DILLARD,[9] interposed to act as a physiological sphincter, may be the answer

Obviously the subject is very far from being exhausted Apart from the necessity for substantial verification of the above findings, many questions may be asked For example, why should some patients, whether they have a hiatus hernia or not, have a competent intrinsic sphincter, and others none? May there be some drug which could restore tone to a lost sphincter, or in reverse could relax the action of one that is too energetic? All in all, it seems that the riddling function of this sphinx remains, particularly when her strangling powers have been lost

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[1] Fyke F E, Jr, Cody, C F, Schlegel, J F *Gastroenterologia,* 1956, 86, 135

[2] Atkinson M, Edwards, D A W, Honour, A, Rowlands, E N *Lancet,* 1957, ii, 1138

[3] Creamer, B, Pierce J W *ibid* p 1309

[4] Cannon, W B Mechanical Functions of Digestion, p 227 New York, 1911

[5] Cross, F S, Kay, E B, Johnson, G F *J thorac Surg* 1957, 34, 736

[6] Olsen, A M, Creamer, B *Thorax,* 1957, 12, 279

[7] *Lancet,* Sept 6, 1958, p 525

[8] Botha, G S M *Brit J Surg* 1958, 45, 569

[9] Merendino, K A, Dillard, D H *Ann Surg* 1955, 142 486

Excision or Resection for Rectal Cancer?

DOES preservation of anal function sometimes jeopardise cure after operation for rectal carcinoma? MAYO et al[1] have compared survivals after anterior resection and abdominoperineal excision, and have found, surprisingly, that 60% of 476 patients traced after anterior resection had survived for five years, compared with 52% of 580 traced after excision It might be suspected that there was bias against excision by the inclusion in the second group of many late cases, but almost exactly half the resection group had metastases (231 cases with, 245 without) compared with rather less than half in the excision group (273 with, 307 without), so the bias, if any, lay against "conservative" resection What then of level?—for surely excision must be a more effective means of cancer clearance when the growth and its metastases lie below the peritoneal reflection? Again surprisingly, the five-year-survival statistics favour resection, not only in the absence but also in the presence of lymph-node involvement, when the lesion was situated in the zone 6-14 cm from the dentate line 2 inches is the agreed minimal length distal to the growth for adequate mural clearance, and conservative resection cannot be performed for growths lower than this It is only fair to observe that the resection group consisted of patients who had been operated on with the hope of cure, and did not include patients who had been operated on with the aim of palliation, whereas there is no evidence that there was such a distinction in the abdominoperineal group

GOLIGHER,[2] though in favour of anterior resection for growths at the rectosigmoid or intraperitoneal part of the rectum, will not countenance its routine use, with the aim of cure, for tumours at a lower level This, in fact, represents the current British view MORGAN[3] has observed that the crude survival-rate of 66% after 110 radical anterior resections for lesions of the intraperitoneal rectum and rectosigmoid, when corrected (81%), is little different from the corrected survival-rate for a comparable group submitted to combined excision (78%) With so little difference as regards survival it is proper to select the operation which is less disabling, and it must be borne in mind that a colostomy is not the only disadvantage of excision—impotence is a sequel in a quarter of the men[4] The experience of BUTLER[5] and of MUIR[6] is similar All agree that resection is the operation of choice for lesions in the upper third That the operation is valuable at lower levels (6-14 cm from the dentate line) for palliative purposes when hepatic metastases are present is not denied, and a case can be made out for its use at this lower level for the aged in all circumstances,[7] since colostomy management is fraught with difficulty in the elderly, who so often live in lonely squalor many rectal growths are slow to develop, and even imperfect eradication may serve the allotted span of an old patient, and the operative risk of resection is lower than that of excision in the elderly Otherwise there are no British advocates of resection as an elective curative procedure at this lower level

Yet the Mayo Clinic is not alone in its reports of favourable results of resection for lesions below the peritoneal cul-de-sac BEST and RASMUSSEN[8] regard it as appropriate for three-quarters of patients with lesions 5-12 cm from the anal margin, and find that survival is comparable to that after excision Furthermore they observe that, whereas excision in their hands is followed by impotence in 75% of cases, after resection the figure is only 25% Nevertheless it is difficult to understand why resection should be as effective as a wider excision in an area where lymphatic spread is known to occur laterally as well as proximally, unless perhaps our conception of the pathological progression is wrong HERMON TAYLOR[9] takes the view that blood-stream spread is the most important factor in prognosis, and that when it occurs it has usually done so before the institution of treatment—thus rendering extensive lymphatic dissection useless This may be so, but it has yet to be demonstrated, though venous invasion has been shown in as many as 50% of specimens[10] As a result of the controversy which has continued throughout the post-war decade, resection is now established as the operation of choice for lesions of the upper third of the rectum In the next decade controversy is likely to centre on the surgical treatment of lesions of the middle third

Contraceptives

THE doctor seeking reliable information on contraceptives has no official source to turn to on this subject the *British Pharmacopœia* is silent Yet the need for informed guidance is great, for some manufacturers may be tempted to make excessive claims, and these are not readily disproved Accordingly the Family Planning Association does a notable public service by publishing its *Approved List of Contraceptives* The contraceptive substances listed must comply with the Association's requirements about quality, efficiency, and harmlessness, and standard of presentation The list, besides being an indispensable source of information for doctors, pharmacists, and nurses, acts as a stimulus to manufacturers to develop effective contraceptives and to present them soberly The latest edition[11] includes an explanation of the purpose of the list and the criteria for approval

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[1] Mayo C W, Laberge, M Y, Hardy, W W *Surg Gynec. Obstet* 1958, 106 695

[2] Goligher, J C *Ann R Coll Surg Engl* 1958 22, 311

[3] Morgan, C N *Proc. R Soc Med* 1957, 50, 1050

[4] Goligher, J C *ibid* 1951, 44 819

[5] Butler, E C. B See *Brit med J* July 26, 1958, p 226

[6] Muir, E G *Aust N.Z J Surg* 1958, 27, 174

[7] Brooke B N See *Brit med J* July 26, 1958 p 226

[8] Best, R R., Rasmussen, J A *J Amer med Ass* 1957, 164, 731

[9] Taylor, H See *Brit med J* July 26 1958, p 226

[10] Barringer P L Dockerty, M B, Waugh, J M, Bargen, J A *Surg Gynec Obstet* 1954 98 62 Madison, M S, Dockerty, M B, Waugh, J M *ibid* 1954, 99 170

[11] Approved List of Contraceptives Published by the Family Planning Association, 64, Sloane Street, London, S W 1 *1s 6d*

Annotations

JOURNEY INTO SPACE

PROGRESS in the exploration of space is rapid. This year we have seen the establishment of satellites in orbital flight around the Earth, and the safe return of two dogs from a height of 279 miles. It seems likely that a multi-stage rocket may soon make the 250,000-mile journey to the Moon.

To place an object in orbit around the Earth, velocities of 18,000 m.p.h. are needed, and to carry an object out of the Earth's gravitational field the velocity of escape must be about 25,000 m.p.h. Rockets, powered conventionally, can attain such speeds only by using large amounts of fuel. The American Vanguard, for instance, needs 1000 lb. of rocket and fuel for every 1 lb. of pay-load. This expensive ratio of propellant-weight to vehicle-weight is at present the most serious impediment to manned space flights. Development of new rocket fuels, possibly nuclear, would render much more feasible a vehicle heavy enough to contain a man with his necessary equipment and yet with power to bring him safely back. At the present rate of progress such a vehicle may be designed within the next few years.

It is reasonable to suppose that man's first journeys into space will be in an Earth satellite, and this will long precede any attempt at inter-planetary travel. Whether man can in fact orbit around the Earth is the first problem which "space medicine" seeks to answer. Space medicine is the youngest of the medical sciences. Fathered by physiology and nurtured by aviation medicine, it has now freed itself of the taint of miscegenation with science fiction. Some aspects of its scope are dealt with in a symposium published in the July issue of the *Journal of Aviation Medicine*.

Conventional powered flight has taken man well above the respirable portion of the Earth's atmosphere, which extends a mere 5 miles. Survival in the tenuous air of the outer atmosphere depends on pressurisation and the maintenance of a high concentration of oxygen. Brief sorties beyond the atmosphere involve no new respiratory problems, except the provision of safety measures if pressurisation should fail or emergency "bail-out" prove necessary. The atmosphere, however, has functions other than the provision of oxygen under pressure. The relatively constant temperature of the Earth depends on its atmospheric shell, the atmosphere also acts as a shield against cosmic and auroral radiation and the assaults of meteors. Man, beyond the atmosphere, will be exposed to extremes of temperature, a yet unknown amount of radiation, and the possibility of collision with meteoric bodies. The intensity and penetrance of the radiations will be of crucial importance in determining the possible duration of exposure of man to these fields.[1] The equipment necessary for protection, for the provision of oxygen, and for pressurisation will impose a weight penalty intolerable with present methods of propulsion.

If space travel is to become a reality, thought must be given to the provision of food and water within acceptable weight limits. On Earth there is a natural cycle for the conservation and re-utilisation of the materials necessary for life. This cycle, involving the passage of individual elements through animals, plants, and bacteria, takes a long time but is complete and self-perpetuating. To economise in weight, some form of closed ecological system for the re-utilisation of all the body wastes must be developed. Clark[2] says "this task of developing an adequate closed food cycle is the most difficult and, hence, the most significant task that must be completed before man can begin extended space voyages". The value of such research is not restricted to space travel. In many circumstances on the Earth and oceans the chances of survival could be increased by artificial systems for recycling human wastes.

The fundamental work on these problems can be undertaken in the laboratory, but the problems associated with increased and decreased gravity are less amenable to a ground experimental approach. During the high-speed take-offs necessary to reach orbiting and free heights, the acceleration forces will impose on the space traveller weights 4-8 times that of gravity. These stresses can be readily simulated on the ground by the human centrifuge, and there is little doubt that, exerted for short periods, they are tolerable: much depends on the position of the person and the clothing worn. On the other hand, the lack of gravity or "weightlessness" which will develop when the space craft becomes a celestial body floating freely in the Earth's gravitational field is far less easily investigated. Gerathewohl and Stallings[3] have succeeded in producing "weightlessness" or zero gravity for short periods by flying an aircraft in parabolic arcs at altitudes of 17,000-25,000 feet. They found that, as predicted, there were disturbances in the otolith organs, which were manifested by ocular illusion. With further investigation it may be found that the psychological and physiological effects of "weightlessness" are intolerable. If this is so it may be possible to provide the space vehicle with some artificial device for producing the sensation of gravity.

HYDATID DISEASE

THE dog is the optimum definitive host of the tapeworm *Echinococcus granulosus*, while the domestic and wild ruminants, and ungulates such as the ox, pig, deer, and *particularly the sheep, are intermediate hosts for the* larval stage or hydatid, which develops in the lungs or liver after the ingestion of ova from an echinococcus-infested carnivore. Man may also ingest the ova, and human hydatidosis has been heavily endemic in certain areas of the world, such as Iceland, New Zealand, Southern Australia, and parts of South America, where an intimate sheep-dog-man relationship prevails. It is not without reason that human hydatidosis has been termed *la maladie des mains sales*.

A long-recognised public-health measure to avert human hydatid disease is to prevent dogs being infected with the tapeworm, and this involves ensuring that the infected viscera of slaughtered animals are destroyed. Dramatic results have been achieved in Iceland and Australia by vigorous promulgation of this policy. Another measure—the regular administration of anthelminthic drugs to every dog—has helped to diminish the regional canine reservoirs of echinococcus.

In Britain hydatidosis in man and domestic animals is relatively rare, the incidence in sheep and in man is highest in South Wales. It is important that this relative freedom from hydatidosis be preserved, and we are therefore disturbed to learn that New Zealand ox livers, containing hydatid cysts have been imported into this country, presumably for pharmaceutical purposes or animal feeding, as many as 3000 bags of livers have been imported in one week, and apparently up to 20% have been infected Even more disturbing is the report[1] that many livers were being disposed of to retail butchers without mention of their diseased condition, it is obvious that small cysts embedded within the liver substance would not readily be detected

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[1] Schaefer, H. J. *J. Aviation Med.* 1958, 29, 492.

[2] Clark, C. C. *ibid.* p. 535.

[3] Gerathewohl, S. J., Stallings, H. D. *ibid.* p. 504.

There seems to be no statutory bar to the importation or sale of these infected livers, provided they are not intended for human consumption, but the Ministry of Health, if satisfied that there is an urgent need in this country for pharmaceutical products manufactured from animal livers, might consider whether it would not be best to insist that the livers be processed in their country of origin An even more serious gap in public-health law is that there is nothing to prevent a retail butcher exhibiting for sale as pet food meat scraps and organs unfit for human consumption, on the same stall as normal sound meat This undesirable practice seems to be growing, and there is urgent need for legislation to make it an offence

ABNORMAL BETA-GLOBULINS

DEVELOPMENTS in the research on abnormal human hæmoglobins in man have been followed by the demonstration of similar polymorphism for other proteins It was known that cow's milk contained two β-lactoglobulins, but this observation had usually been made on pooled milk When samples from individual animals were examined it was found that the two lactoglobulins were distributed as polymorphic characters, some cows producing only one of the two globulins and others both—representing homozygous and heterozygous phenotypes [2 3] In the plasma of man there are two haptoglobins [4]—α_2-globulins capable of binding free hæmoglobin [5]—which also are distributed as if they are determined by allelic genes Smithies [6 7] also found in human plasma three different β-globulins which he called β-B, β-C, and β-D There is evidence that the formation of these three β-globulins is genetically controlled, and Smithies suggests that each may be determined by one of three allelic genes He observed the patterns C, BC, and CD C was most commonly found in the Canadians he investigated, but C plus B occurred in 1% of Canadians and C plus D in about 4% of American Negroes The phenotype CD was even commoner in Australian aboriginals, in whom one example of a fourth phenotype (D) was discovered [8] The phenotypes B and BD, which are also possible, have so far not been described

Harris et al [9] working in Britain, have studied the β-globulins of man by means of the discontinuous buffer system of Poulik [10] In a series of 153 Africans from the Gambia they found four examples of CD Two types of D β-globulin were identified which differed slightly but distinctly from one another in their electrophoretic behaviour, these have been named D_1 and D_2 In 139 English people no examples of the CD_1 or the CD_2 phenotype were found, but the combination B plus C was found in two people The two B β-globulins were not identical, so there seem to exist a B_1 and a B_2 The family of the person with the B_1C phenotype was further investigated, and a pedigree was constructed which showed that the β-globulin B_1 is genetically determined, and that the members of the family with the B_1C phenotype are heterozygous for the appropriate gene.

Obviously the human serum β-globulins deserve to be studied with the close attention that has been given to the hæmoglobins, they are likely to be of equal interest to the biochemist, the geneticist, and the anthropologist Polymorphism is the outcome of the selective advantages and disadvantages in a particular environment of inherited characters which are determined by allelic genes and which are neither dominant nor recessive in the phenotype In the case of the hæmoglobins much interest has been taken in the resistance of carriers of the trait for sickle-cell hæmoglobin against the lethal effect of malignant malaria It will be of special interest to see which selective advantages the various β-globulins confer against diseases due to infection, climatic influences, and malnutrition. A polymorphism for serum-β-globulins has also been demonstrated in cattle,[11 12] in which there are three different proteins determined by a three allele system resulting in six phenotypes In cattle the geographical distribution of one of the β-globulins suggests that it is associated with tolerance of the more severe northern climates

THE "MEDICAL OFFICER"

As an independent journal "for medical men and women in the Government and municipal services"—a group which, though influential, is not large—the *Medical Officer* has attained its golden jubilee [13] only because it has always been so well worth reading The difficulties of producing a weekly journal for a small group are very real, and this is the only public-health weekly in the world, but the benefit to readers is real too, for a periodical which comes out once a week can "combine some of the liveliness and topicality of a newspaper with the more sober and lasting qualities of a scientific journal." The particular attractiveness and value of the *Medical Officer* derives largely from the Elliston family, its hereditary editors George Elliston, son of a physician in Ipswich and nephew of the first M O H for that town, was on the staff of Sir Joseph Causton & Sons, the printers, when he founded the journal in 1908, and later, as secretary of the Society of Medical Officers of Health, member of Parliament, chairman of the health committee of the City of London, chairman of the board of management of the London School of Hygiene, and in many other ways a power in public health, he was a remarkably well-informed as well as a naturally able editor—with what his old friend Sir Allen Daley describes as "the journalistic 'nose' for finding out any unusual development and the barrister's flair for pungent exposition" Since Sir George Elliston's death in 1954, his eldest son, Mr Lewis Elliston, who had long been working with him, has carried on the journal with the same mixture of perception, friendliness, and zest We wish it many more years of its valuable service to medicine

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Prof R H S THOMPSON, Prof E J WAYNE, and Prof B W WINDEYER have been appointed members of the Medical Research Council

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Lieut -General Sir BENNETT HANCE, medical adviser to the Commonwealth Relations Office and a former director-general of the Indian Medical Service, died on Sept 5 at the age of 71

Prof W M FRAZER, medical officer of health for Liverpool from 1931 to 1953, died on Sept. 8 at the age of 70

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[1] *Times*, July 5, 1958
[2] Aschaffenburg, R., Drewry, J *Nature Lond* 1955, 176, 218
[3] Aschaffenburg R, Drewry, J *ibid* 1957 180, 376
[4] Smithies, O, Walker, N F *ibid* 1955, 176, 1265
[5] Polonovski M Jayle M F *Bull Soc Chim biol*, *Paris*, 1939 21, 66
[6] Smithies, O *Nature Lond* 1957, 180, 1482.
[7] Smithies O *ibid* 1958, 181, 1204
[8] Horsfall W R., Smithies O *Science*, 1958, 128, 35
[9] Harris H, Robson, E. B, Siniscalco M *Nature, Lond* 1958, 182, 542.
[10] Poulik M. *ibid* 1957, 180, 1477
[11] Ashton, G C *ibid* p 917
[12] Ashton, G C. *ibid* 1958, 182, 370
[13] *The Medical Officer* 72, Fleet Street, London, E.C.4 Golden jubilee number, Sept. 5, 1958

Special Articles

THE COST OF ORAL IRON PREPARATIONS IN FAMILY AND IN HOSPITAL PRACTICE

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TWENTY years ago Davidson and Fullerton (1938) clearly established that, for correcting iron-deficiency anæmia, ferrous sulphate was as effective as any of the iron preparations then available (ferrous carbonate, ferrous chloride, colloidal iron, iron and ammonium citrate) and had a considerable advantage in cost During the past ten years a number of organic preparations of iron have appeared on the market and gained wide popularity Further studies have therefore been undertaken to ascertain which oral preparation is the most suitable in regard to therapeutic efficiency, incidence of toxic effects, and cost

A therapeutic trial by O'Sullivan, Higgins, and Wilkinson (1955) showed that when ferrous sulphate, ferrous gluconate, or ferrous succinate was given in doses containing equivalent amounts of elemental iron (210 mg daily), each caused a similar rise in the hæmoglobin level

Kerr and Davidson (1958a and b) have recently reported the results of two controlled investigations In the first, ferrous sulphate, ferrous gluconate, ferrous gluconate plus vitamin C, and control tablets containing lactose were administered to groups of women in the last trimester of pregnancy The amount of elemental iron given daily in each preparation was 105 mg The mean rise in the hæmoglobin level in the three groups receiving the iron-containing tablets was approximately similar, and there was no difference in the incidence of gastrointestinal "side-effects" between these three groups or between the treatment groups and the control group In a second trial ferrous sulphate, ferrous gluconate, ferrous succinate, ferrous calcium citrate, and control tablets containing lactose were administered in turn to groups of nurses With the dosage of iron given, none of the iron-containing preparations caused more side-effects than the control tablets By using known and unknown control tablets it was established that the symptoms complained of by the nurses were mainly psychological in origin

Both in family and in hospital practice, iron-deficiency anæmia is one of the diseases most commonly encountered, and very large amounts of iron are prescribed annually for its treatment The choice of oral iron preparation is determined partly by the doctor's own clinical experience and partly by the pressure of advertising. Since ferrous sulphate, ferrous gluconate, and ferrous succinate, when given in tablets containing equivalent amounts of elemental iron, have similar therapeutic efficiency and similar toxicity, the problem of their relative cost assumes great importance This is particularly the case today when there is an urgent need for economy in the National Health Service

Accordingly, we have inquired into the comparative costs of the widely used non-proprietary and proprietary iron tablets, and the frequency with which they are prescribed

Comparative Cost of Various Iron Tablets

Information about the cost of the more popular iron tablets in present use in family practice is summarised in table I The four proprietary preparations are designated "proprietary 1, 2, 3, and 4"

Column A shows the basic price of 100 tablets Because of the system of costing, the allowance which the chemist receives from the Government for the purchase price of a drug used in dispensing N H S prescriptions is not always the same as the net cost Hence the former figure has been given The prices of non-proprietary preparations have been obtained from the National Health Service, Scotland, Drug Tariff (January, 1958) and Amendments (to April, 1958), and those of proprietary preparations from The Retail Chemist Trade Price List of Proprietary Articles (1957) and Supplements (to March, 1958), the latter prices being adjusted to accord with the Drug Tariff system of payment

Most iron preparations are cheaper to the chemist if purchased in bulk For proprietary preparations deduction is made if the chemist endorses the prescription to the effect that he has dispensed the 100 tablets from a larger pack Throughout the table, therefore, the reduced cost of 100 tablets of the proprietary preparations if dispensed from a 1000 pack is shown in parentheses For non-proprietary preparations, however, the figure shown in column A is always paid, regardless of the size of pack In some circumstances the proprietary preparations are subject to 30% purchase-tax Purchase-tax has not been included in the prices given in column A, but where applicable has been listed separately in column B

Column C gives the total amounts which the chemist receives for dispensing 100 tablets on an N H S (Scotland) prescription These figures (to the nearest halfpenny) have been derived as follows

Net cost of 100 tablets (column A) plus oncost allowance (25% of net cost), plus 1*s* 7*d* dispensing fee, plus 1$\frac{9}{10}$*d* container allowance, plus refund of purchase-tax if applicable

The cost to the N H S in Scotland of a prescription for 100 tablets of each of the iron preparations is shown in column D This amount is the figure given in column C minus 1*s* (the prescription charge paid directly to the chemist by the patient)

The prices to patients of 100 iron tablets if purchased at a chemist's shop without a prescription are listed in column E

TABLE I—COMPARATIVE COST OF 100 TABLETS OF DIFFERENT ORAL IRON PREPARATIONS

Oral iron preparation	A Basic price of 100 tablets of different oral iron preparations	B Purchase tax on 100 tablets	C Allowance to Chemist for dispensing 100 tablets on N H S prescription	D Cost to N H S of prescription for 100 tablets (column C minus 1*s*)	F Cost to patient of 100 tablets if purchased at chemist's shop without a prescription
Ferrous sulphate					
Ferrous sulphate tablets *B P*	1*s* 3½*d*		3*s* 4½*d*	2*s* 4½*d*	2*s* to 3*s*
Ferrous-sulphate compound tablets *B P C*	5*d*		2*s* 3*d*	1*s* 3*d*	1*s* 3*d* to 2*s*
Proprietary 1	1*s* 0½*d* (4*d*)	3½*d* (—)	3*s* 4½*d* (2*s* 2*d*)	2*s* 1½*d* (1*s* 2*d*)	1*s* 10*d*
Ferrous gluconate					
Ferrous gluconate tablets *B P C*	2*s* 5*d*		4*s* 9*d*	3*s* 9*d*	4*s* to 5*s*
Proprietary 2	3*s* 10*d* (2*s* 9½*d*)	(—)	6*s* 6½*d* (5*s* 3*d*)	5*s* 6½*d* (4*s* 3*d*)	7*s* 4*d*
Proprietary 3	3*s* 1½*d* (3*s* 1½*d*)	11½*d* (—)	6*s* 7*d* (5*s* 8*d*)	5*s* 7*d* (4*s* 8*d*)	5*s* 9*d*
Ferrous succinate					
Proprietary 4	3*s* 1½*d* (2*s* 5*d*)	11½*d* (8½*d*)	6*s* 7*d* (5*s* 6*d*)	5*s* 7*d* (4*s* 6*d*)	5*s* 5*d*

Figures in parentheses denote reduced cost of 100 tablets if dispensed from a 1000 tablet pack

TABLE II—SURVEY OF NATIONAL HEALTH SERVICE PRESCRIPTIONS DISPENSED IN SCOTLAND DURING MAY, 1957

Total number of N H S prescriptions dispensed=1,689,505

Number of prescriptions in sample studied=10,495 (0 6% of total)

Number of prescriptions for oral iron preparations in sample =230 (2 19% of sample)

Number of prescriptions for different oral iron preparations and number of tablets prescribed

Oral iron preparation	No of prescriptions	Total no of tablets prescribed	Average no of tablets per prescription
Ferrous sulphate			
Ferrous-sulphate tablets *B.P*	23 (*10%*)	2268	98 6
Ferrous-sulphate compound tablets *B P C*	14 (*6%*)	1466	104 7
Proprietary 1	17 (*7%*)	1550	91 2
Total	54 (*23%*)	5284	
Ferrous gluconate			
Ferrous-gluconate tablets *B.P C*	39 (*17%*)	3176	81 4
Proprietary 2	61 (*27%*)	5196	85 2
Proprietary 3	14 (*6%*)	1068	76 3
Total	114 (*50%*)	9440	
Ferrous succinate			
Proprietary 4	62 (*27%*)	5732	92·5

Total number of iron tablets prescribed in sample=20,456

Average number of tablets per prescription in sample=88 9

Ratio of prescriptions for ferrous sulphate to prescriptions for ferrous gluconate plus ferrous succinate=1 (23%) 3 (77%)

Ratio of prescriptions for non-proprietary preparations to prescriptions for proprietary preparations=1 (33%) 2 (67%)

For proprietary preparations the retail price is fixed by the manufacturers For non-proprietary preparations the figures given represent the average prices charged by several chemists in Edinburgh at whose shops inquiry was made

This table shows that the cost to the Government of a prescription for 100 ferrous-sulphate tablets ranges from 1*s* 2*d* to 2*s* 4½*d* For ferrous gluconate the range is 3*s* 9*d* to 5*s* 7*d* and for ferrous succinate it is 4*s* 6*d* to 5*s* 7*d* If a patient purchases 100 iron tablets at a chemist's shop without a prescription the price charged will vary from 1*s* 3*d* for "Ferrous sulphate compound tablets *B P C*" to 7*s* 4*d* for one of the proprietary preparations of ferrous gluconate The cost to a patient of 100 iron tablets dispensed on a "private" prescription varies from chemist to chemist, but is usually more than the cost of the same preparation purchased over the counter or supplied on a N H S prescription

The difference in cost of oral iron preparations to the hospitals is still more striking Since most preparations are supplied to hospitals by manufacturers under contracts which are confidential, the full range of prices cannot be quoted Furthermore, the expenditure on iron tablets may be greatly reduced if very large quantities are purchased Hence the cost of iron tablets is relatively less in a large hospital which caters particularly for acute medical, surgical, and obstetric cases than in a small hospital which caters for the chronic sick We are satisfied, however, from information received from hospitals and manufacturers that the price to hospitals of proprietary and non-proprietary preparations of ferrous sulphate is only 3*d* to 4*d* per 100 tablets, whereas ferrous gluconate costs at least three to six times as much and ferrous succinate six to ten times as much

Frequency with which Different Iron Tablets are Prescribed

Family Practice

In a survey undertaken by the Department of Health for Scotland of 10,495 N H S prescriptions dispensed by representative chemists throughout Scotland during the month of May, 1957, it was found that 2 19% (230) of the prescriptions were for iron tablets This is in agreement with the observation of Dunlop, Inch, and Paul (1953) that about 3% of their large sample of prescriptions dispensed in Scotland during October, 1951, were for iron—a figure which included mixtures and injections as well as tablets Table II shows the frequency with which different preparations were prescribed and the average number of tablets ordered The terms "proprietary 1, 2, 3 and 4" refer to the same preparations as in table I

Only 23% of the prescriptions dispensed in family practice were for ferrous sulphate The remainder were for ferrous gluconate (50%) and ferrous succinate (27%) Two-thirds of the prescriptions were for proprietary preparations of iron ferrous sulphate (proprietary 1) 7%, ferrous gluconate (proprietary 2 and 3) 33%, and ferrous succinate (proprietary 4) 27%

During the month under consideration (May, 1957) 1,689,505 N H S prescriptions were dispensed in Scotland Although the sample studied represented only 0 6% of these, it probably gives a fair indication of the pattern of prescribing, since the prescriptions were obtained by random sampling If this is so, the total number of N H S prescriptions for oral iron tablets for family practice in Scotland in a typical month will be about 38,000 $\left(\frac{203\times 100}{0\ 6}\right)$, and, since the average number of tablets ordered per prescription is about 90, the total number of iron tablets dispensed per month is between 3 and $3^{1}/_{2}$ million

Hospital Practice

The number of hospital beds in Scotland is 65,802 (May, 1958), of which 22,036 are in mental hospitals A questionnaire was sent to ten general hospitals in different parts of Scotland, and (because a large proportion of beds are for mental patients whose iron requirement was thought likely to be low) to four large mental hospitals Information was requested regarding the quantities of ferrous-sulphate, ferrous-gluconate, and ferrous-succinate tablets, both proprietary and non-proprietary, used in a recent twelve-month period The replies are summarised in table III There was considerable variation in the prescribing habits in the different hospitals, but, taking them as a whole, ferrous gluconate seems to be used

TABLE III—SURVEY OF THE USE OF IRON TABLETS IN A RECENT 12-MONTH PERIOD IN REPRESENTATIVE HOSPITALS IN SCOTLAND

—	No of beds in Scotland	No of beds surveyed	% of total no of beds	No of iron tablets used annually			Total
				Ferrous sulphate	Ferrous gluconate	Ferrous succinate	
General hospitals	43,766	8,010	18 3	810,000*	815,000	135,000	1,760,000
Mental hospitals	22,036	4,063	18·4	44,000	37,000	1000	82,000
Total	65,802	12,073	18 3	854 000 (*46%*)	852,000 (*46%*)	136,000 (*8%*)	1,842,000

* The figures for numbers of iron tablets are to the nearest thousand.

almost as often as ferrous sulphate, and, although ferrous succinate has not gained wide popularity, large quantities of it are also being prescribed

If the hospitals which cooperated in the survey are typical of the remainder, the total number of iron tablets consumed annually by hospital patients in Scotland is likely to be about 10 million, of which 46% are ferrous sulphate, 46% ferrous gluconate, and 8% ferrous succinate

Summary and Conclusions

Ferrous-sulphate tablets, with or without added trace elements, proprietary or non-proprietary, are the cheapest preparations of iron at present available for oral medication Since ferrous sulphate raises the hæmoglobin level as effectively as ferrous gluconate and ferrous succinate, and, when given in comparable doses of elemental iron, is no more liable to cause side-effects it is the preparation of first choice for oral iron therapy

In hospital practice the amount of ferrous sulphate prescribed (46%) is slightly less than the total for the newer organic preparations (54%) The prices of the different tablets vary considerably, depending on the manufacturer and on the quantity purchased, but, using the lowest price for each preparation, the cost of iron tablets to the hospital service in Scotland each year can be calculated to be at least £3000

In family practice, however, ferrous sulphate is prescribed considerably less frequently (23%) than the more expensive organic preparations of iron (77%) From the data present in this paper the cost of the iron tablets used by the National Health Service in Scotland is calculated to be £6500 per month

If ferrous sulphate were always prescribed in preference to ferrous gluconate and ferrous succinate the saving to the N H S in Scotland would be, at a conservative estimate, about £1800 in a year for hospital practice and £3250 a month for family practice—a total of almost £40,000 per annum

If it is accepted that the ferrous compounds mentioned above are similar in therapeutic efficiency provided that the daily intake of iron in each preparation is the same, and if it is agreed that the standard effective dose of ferrous sulphate is one tablet three times daily (180 mg of elemental iron), then the equivalent dose of ferrous gluconate and ferrous succinate would be five tablets per day (175 mg of elemental iron) On this basis the use of ferrous sulphate would lead to an even greater saving to the Health Service than the amounts suggested above

We wish to thank Sir Kenneth Cowan, of the Department of Health for Scotland, for giving us permission to publish the prescription survey and for providing details of the number of hospital beds in Scotland We are also grateful to those physicians and pharmacists in different parts of Scotland who supplied us with data regarding the iron tablets used in their hospitals

REFERENCES

Davidson, L S P , Fullerton, H W (1938) *Edinb med J* 45, 193
Dunlop, D M , Inch, R S , Paul, J (1953) *Brit med J* i, 691
Kerr, D N S , Davidson, L S P (1958a) *Lancet*, ii, 483
— — (1958b) *ibid* p 489
National Health Service, Scotland, Drug Tariff (1958) and Amendments H M Stationery Office
O'Sullivan, D J , Higgins, P G , Wilkinson, J F (1955) *Lancet*, ii, 482
The Retail Chemist Trade Price List of Proprietary Articles (1957) and Supplements London

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CONSULTANTS AND OTHER SPECIALIST STAFF IN HOSPITALS

THE Ministry of Health and Department of Health for Scotland have issued tables that will be of special interest to those intending to train as specialists

Table I (not reproduced here) shows the age-distribution at June 30, 1956, of consultants and senior hospital medical officers practising in the various specialties It shows also the numbers of paid sessions undertaken by the consultants and S H M O s in each specialty for each year of birth

Table II shows the numbers of consultants in each of the specialties year by year from 1949 The corresponding figures for senior hospital medical officers are not available

Table III shows the number of senior registrars in each specialty on June 30, 1956, at the various stages of their training The column headed "Others" includes those holding "transitional" posts

All the figures relate to England, Wales, and Scotland

TABLE III—SENIOR REGISTRARS IN GREAT BRITAIN ON JUNE 30, 1956

Specialties	Training plan					Others*	Grand total
	1st year	2nd year	*3rd year*	4th year	Total		
General medicine	39	40	30	27	136	68	204
Diseases of the chest	12	18	11	8	49	4	53
Mental health	49	32	20	9	110	12	122
Neurology	2	3	2	5	12	2	14
Pædiatrics	4	8	7	5	24	12	36
Radiology	25	15	16	8	64	3	67
Radiotherapy	4	5	4	3	16		16
Physical medicine	3	4	2	1	10		10
Pathology	16	17	14	16	63	40	103
Infectious diseases	2	1		1	4	2	6
Dermatology	2	3	4	7	16	13	29
Venereology	1	1	1	1	4	2	6
Ophthalmology	19	18	12	5	51	11	62
General surgery	47	41	31	26	145	66	211
Anæsthetics	39	19	11	4	73	6	79
Neurosurgery	2	6	2	2	12	3	15
Plastic surgery	1	4	2	2	9	8	17
Thoracic surgery	5	5	6	3	19	10	29
Orthopædic surgery	22	18	8	6	54	11	65
Ear, nose, and throat surgery	17	9	9	5	40	7	47
Obstetrics and gynæcology	17	24	17	9	67	34	101
Totals	328	291	209	153	981	314	1295

* Includes 93 honorary and 26 part-time senior registrars

TABLE II—NUMBER OF CONSULTANTS IN EACH SPECIALTY AT VARIOUS DATES SINCE DEC 31, 1949 (GREAT BRITAIN)

Date	General medicine	Diseases of the chest	Mental health	Neurology	Pædiatrics	Radiology	Radiotherapy	Physical medicine	Pathology	Infectious diseases	Dermatology	Venereology	Ophthalmology	General surgery	Anæsthetics	Neurosurgery	Plastic surgery	Thoracic surgery	Orthopædic surgery	Ear, nose, and throat surgery	Obstetrics and gynæcology	Totals
Dec 31, 1949	755	216	449	53	166	327	85	49	495	50	127	89	331	927	496	37	30	49	252	312	424	5719
Dec. 31, 1950	831	250	504	53	202	378	93	57	526	52	136	101	311	943	602	39	32	57	269	328	439	6233
Dec. 31, 1951	857	266	532	59	208	400	101	61	541	49	135	99	342	918	655	42	33	66	293	311	419	6476
Dec. 31, 1952	904	310	566	61	214	414	108	70	581	51	142	97	351	986	714	44	36	81	320	339	473	6662
Dec 31, 1953	905	340	595	67	222	436	112	75	631	60	145	91	342	982	748	46	43	89	328	346	473	7079
Dec 31, 1954	924	344	616	68	226	447	116	74	646	59	146	93	340	987	782	49	45	91	335	350	495	7225
June 30, 1955	932	346	633	69	228	455	120	73	659	58	146	93	341	998	797	49	50	93	339	353	493	7315
June 30, 1956	946	347	640	70	229	468	127	77	689	56	150	92	339	988	815	52	50	97	353	347	495	7427

Consultants practising in more than one specialty have been included under each Table includes honorary consultants

HOSPITAL COSTS

In England and Wales the cost of our hospitals has grown from £219 million in 1949–50 to an estimated £421 million in the present financial year This is a colossal sum, but the gross national product—the most straightforward measure of the country's total resources—has risen even more rapidly, as was clearly shown by Abel-Smith and Titmuss[1] Part of the increased cost merely reflects the falling value of the pound But other factors are at play First, the population of England and Wales has increased in the past ten years Secondly, there are more elderly people in the country, and their demands on hospital services are greater than those of the general population Thirdly, the hospital service has been slightly expanded, and it is dealing with many more patients Staffed beds have increased in the decade from 448,057 to 476,870, and admissions have increased from 2,937,000 in 1949 to 3,794,000 in 1957 Fourthly, the length of stay, especially in maternity and mental cases, has been curtailed, people are getting well faster, and it is usually the early days of hospital care, when so much diagnostic work has to be done, that cost the most Finally, modern hospital techniques are more expensive than those of former years

NEW YORK

So much for the local scene, but England and Wales are not the only countries with problems of cost In the New York area the seventy-four voluntary hospitals and convalescent homes report an operating loss of $23,500,000 for 1957—an increase of $3,550,000 over the 1956 figure[2] This deficit takes no account of, on the one hand, receipts from philanthropic sources and income from investment and, on the other, hospital depreciation, interest on debts, and money spent on research and medical education It was estimated that the hospitals' net loss, including all income, was in the region of $6 million, this estimate includes an allowance of 5% for plant depreciation Meanwhile the operating income, including revenue from patients and from auxiliary activities which produce income, went up 6 8% to $176,000,000, and the operating costs rose 8% to almost $200 million

In the New York area hospital admissions have increased by 41% since 1946 In the production of motor-cars, the greater the number that run along the production line, the lower the cost of each, but in hospital service the reverse holds good speed and skill add to the expense Obviously no-one would want to change this beneficent advance, and, as one administrator said, "the deficit is a badge of honour" But hospital care, like pleasure, has to be paid for some time or another Many administrators in the New York hospitals and elsewhere feel that, if only the potential patients could be taught to appreciate the benefits of scientific care in reducing the period of illness, as well as cutting down suffering and anxiety, they would be ready to pay the enhanced price Dr Martin Steinberg, the executive director of Mount Sinai Hospital, says this[2]

> "One cannot define hospital service in terms of so many dollars a day or in terms of a specific quantity When the patient purchases hospital services, the quantity and its cost are determined only by the requirements of his illness and the capacity of the hospital to fulfil them"

But this partly begs the question Admittedly some patients would be able, and even more would be willing if they were able, to pay enhanced costs, but what about the many for whom the hospital bill spells ruin, or at least a crippling reduction of income, perhaps at the very time when extra benefits of food and fresh air are most desirable?

CANADA

The problem of hospital costs has been faced realistically in several of the Provinces of Canada The *Journal of the Canadian Medical Association* has issued the report of an interesting and instructive symposium which deals with various approaches[3]

Alberta

In Alberta[4] the first step towards hospital insurance was to establish a free public-ward service for all maternity cases This was heartily approved by the public, because the overwhelming majority of the women have their babies in hospital The profession also gave considerable support to the plan The next stage was to introduce what became known as the "dollar-a-day" plan, through which each patient pays that amount for a public-ward bed, the remainder of the cost being met by the municipality with help from the provincial Government The people strongly supported the scheme, but there was some resistance from the municipalities on the ground that the provincial contribution was not enough Nevertheless the entire province was covered within two years

This advance into the realm of public medical care was in time felt to be insufficient Many patients still had a heavy hospital bill to discharge on account of the cost of medicines, operating-room charges, and diagnostic services By 1945 these extras were absorbed by an additional flat-rate charge of a dollar a day, and this extension in its turn proved highly popular The waiting-lists became longer—in relation to short-term investigation up to as much as 22%

Saskatchewan

In Saskatchewan[5] the Hospital Services Plan has been in operation since 1947 The scheme was designed to remove the financial deterrent to hospital care and also to ensure that the hospitals received enough funds to provide an adequate service Most persons who have lived in the province for six months are required to join the scheme, unless they already qualify for complete hospital care through other approved plans Those taking part represent more than 92% of the population The one test is the need for hospital care, and the Plan pays for public-ward accommodation and all incidental costs such as X-ray, anæsthetics, and physiotherapy At the beginning of 1957 the limit was raised to $10 per day In the same year the hospital tax was fixed at $20 for self-supporting persons, with $5 for dependent children The maximum tax payable per family was increased to $45

On the whole the Plan has worked very well although it contributes little towards the capital costs of construction or extension, beyond the federal grants of $2000 per active bed and $1500 for each convalescent bed These grants have been matched by the provincial Government. The Plan is administered by the Department of Public Health and by staff employed by the Government The Hospital Association and the medical profession are purely advisory

In 1956 the average number of days in hospital for all patients was 10 4 Patients remaining in hospital for over thirty days represented 5% of all cases, and yet accounted for more than 31% of the patient-days This emphasises the need for more studies on the treatment of long-term illness, and especially on the care of these patients, wherever possible, outside the " acute " wards of the general hospital

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[1] Abel-Smith, B , Titmuss, R. M *The Cost of the National Health Service in England and Wales* London, 1956

[2] *N Y Times*, June 2, 1958

[3] *Canad med Ass J* 1958, 78, 747–773

[4] Morgan, H. V *ibid* p. 747

[5] Brown, J L *ibid* p 749

In 1947 the total expenditure on the Plan was about $7 5 million By 1956 the figure had risen to over $22 million, and the average cost per case (excluding the newborn) rose in these ten years from $46 61 to $124 46

British Columbia

The main features of the arrangements in British Columbia are as follows [6]

1 All persons, after a year's residence, are entitled to hospital benefits

2 Payments cover the acute phases of hospital care but not chronic illness,

3 Standard ward care which is covered includes the use of the operating-room and nearly all drugs and services except anæsthetics

4 For outpatient services required within twenty-four hours after an accident a charge of $2 is made

5 Inpatients (except welfare cases) are charged a coinsurance-rate of $1 per day

6 There are limited insurance benefits for residents of British Columbia who have to enter hospitals outside the province

In the early days of the scheme attempts were made to levy individual premiums and, later, to make payroll deductions, but in 1954 these were replaced by payments from general taxation by means of raising the social-service tax from 3% to 5%

In summing up the effects of Government-financed hospital insurance in British Columbia Watson [6] makes the following points in relation to hospital costs

> A look at the " business " growth of the insurance scheme shows an expanding picture Since 1948 hospital beds have increased by 37%, patient-days by 50%, and staff by 80% During the same period expenditure on hospital insurance has risen well over 100% On the other hand, salaries and wages have gone up 225% " The doctor, thinking of medical services and not of the big business statistics, sees a lop-sided progress The hospitals have been helped out of debt Their staff has increased The hospital worker has had his standard of living increased remarkably Ironically, however, the beds available, the patients treated and the diagnostic and therapeutic advances have accounted for the smallest percentage of the increase "

Federal Legislation

The position in Canada is likely to change as a result of the Hospital Insurance and Diagnostic Services Act of 1957 [7]

> This enabling measure provides for a contribution by the Federal Government of 50% of the cost, more or less, to any province which agrees to make insured hospital services available, on uniform terms and conditions, to all residents of the province so entitled under provincial law, and without charge to the residents except *a general charge by way of premium*, or other amount unrelated to a specific service, and except authorised charges The Act does not cover hospitals for the tuberculous or the mentally ill Capital expenditure and debts are also excluded Each province will decide how it will raise its share of the costs—whether by premium or taxation

One effect is likely to be an increased demand for hospital care—up to a " plateau " estimated at about 7–8 beds per 1000 population

WIDER LESSONS

These findings direct attention to matters requiring further consideration in Britain and other countries First, we must be ready to examine hospital costs on a basis which offers real opportunities for comparison between one country and another Secondly, the rise in costs should be carefully related to other features in the national economy, including the general increase in prices, the growth of population and the demand for institutional services, and, not least, the urge towards higher standards of living It is by no means easy to devise criteria of cost which will satisfy the demand for accurate comparison between one country and another, but the idea is worth far more than a passing glance

Such a study should help us to detect economies that might be made without loss of efficiency, and particularly the point at which hospital care could well be exchanged for home care We might then be better able to decide what types of patient could be transferred, on good medical grounds, from the highly specialised attentions of the " acute " ward to simpler and perhaps more appropriate accommodation

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The Wider World

MEDICINE IN THE NEW INDIA

R E Rewell
M D Lond, M R C P
PATHOLOGIST, THE WOMEN'S HOSPITAL, LIVERPOOL

For two years, from early 1956 until early 1958, I was in India, having been invited there under the Colombo Plan Working entirely among Indians, with Indians and for Indians, and counting as a class I officer of the Government of India, I obtained an insight into medicine in the country such as is not possible for anyone paying a brief visit

Western medicine on the British model has been established in India for a long time for example, the Government General Hospital in Madras claims to have been founded in 1677, and much of the present building was designed by Florence Nightingale British methods of teaching predominate, British textbooks are used, and English is still the medium of instruction The present generation of educated people think and talk in English, and this language is unlikely to be replaced by Hindi for a long time, especially in South India where Hindi is regarded as the more foreign

Indeed British methods persist in every activity, especially in government and administration and perhaps it is the persistence of this edifice that has prevented the country from sinking into chaos Unfortunately, however, the system was not designed to give freedom at the periphery, and the vested interests of people who have been in it for a long time have increased its rigidity Europeans long in the country told me how little was the difference to them when the few British at the top were replaced by Indians, and indeed there were *few to replace* 77% of foreign investment in India is British, and the number of British technicians and business administrators in the country is greater than ever Indians regard the British domination as one episode in their country's long history—inevitable in the circumstances and nothing to be ashamed of Newspapers always *refer to their present* " independence ", and there is no double talk of " freedom " or " liberation " Sastri [1] presents the background to this

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[6] Watson, H N *ibid* p 751

[7] See Turner, J G *ibid* p 768

[1] Sastri, K A N A History of South India London, 1955

British policy in medicine has been continued in many ways. Thus one of the recommendations of the committee on the medical services, formed in 1941 with Lieut.-General Sir Bennett Hance as chairman, was that institutes for postgraduate training should be established throughout the country, where there were suitable facilities and teachers, and these are now being set up. The Institute of Obstetrics and Gynæcology is at the Government Hospital for Women and Children in Madras and I was invited there as first professor of pathology. It was intended originally that these institutes should eventually move to Delhi and form part of a central Institute of Medical Sciences, but now a much smaller central institute is starting up, while the peripheral ones are to continue.

Some improvements in the organisation of medicine have been introduced recently by the central Government. Thus the standard of the qualifying examinations has been made uniform at an internationally accepted level. The diplomas of the various States have been abolished, retaining only the M.B. of the universities, and central inspection of the examinations has been undertaken. There is, of course, reciprocity with many Commonwealth countries. A number of new colleges have been opened, new buildings being erected, and senior staff trained specially, many of them abroad. Though unable to visit any of these colleges, I heard much about them from younger colleagues who hoped to transfer to them.

THE DOCTORS

The doctors among whom I was working were a hand-picked bunch, but I found the general standard of medicine higher than I had expected. In his own surroundings the Indian is far more adaptable and resourceful than he often appears in an alien environment, nor is he as self-conscious. After the first shyness had worn off I found postgraduates well informed and energetic in discussion, and, as with us, methods of teaching are far more by informal rounds and discussions than by formal precept and lecture. The Indian doctor works among ignorant and depressed people who regard him as a superior being, patients are too poor to pay much and there is heavy competition from cheap quacks. (These include practitioners of Ayurvedic "medicine", a system based on the old humours[2] but encouraged by the Government.) It is surprising, then, that almost all the doctors remain keen and alert and continue to think of what will be best for the individual patient. They tend to emphasise their membership of the international army of medicine at the expense of local knowledge: thus they will quote British and American statistics when these are not applicable (although often there are no comparable Indian figures). However, they know well enough the circumstances of their own compatriots and I myself found that adaptation of Western knowledge to the social conditions of the patients was not difficult, given a readiness to inquire and to learn. Indians of education are very willing to help in this, and do not object to inquiries made in the proper spirit, even when concerning religion. I heard of an understandable tendency among undergraduates to regard the humble villager as a lower species, but this is evidently soon rectified by the chastening discipline of practice.

I was told that there are about three times as many candidates as places at the medical schools. A fifth are reserved for women and others for members of the "scheduled castes". The curriculum is based firmly on the British model. Some interesting experiments with it are being made at the Christian Medical College at Vellore, but this, like all missionary enterprises now, works under a strong and continuous barrage of criticism and discouragement from the Government. The whole concern is a free gift from private individuals in America, Australia, and Britain, and its senior staff is drawn from those countries, but its achievements are claimed as "Indian".[3]

CONDITIONS OF WORK

Government schemes are by no means all helpful to progress. Not only is the administration rigid but the Oriental genius for red tape and procrastination, especially over finance, has to be experienced to be believed. My own work was much curtailed by this.

Most unfortunately the semi-military control of personnel has been retained, and even senior people are "posted" (with no warning and without being consulted) by the D.M.S. who rules the medical service of each individual State in the Indian Union.

Promotion is entirely by seniority within a specialty, there is virtually no competition for appointments, and in a hospital all authority is in the hands of the senior member of the staff as superintendent. Because people are moved so often, the staff of a hospital becomes quite unstable in its composition. Even at the earliest stage, trainees are "selected" arbitrarily for the various courses or appointments that will lead to higher degrees. Unless one is chosen in this way, one has no chance of specialising within the hospital service. Except for those still belonging to missionaries, all the free hospitals, including the teaching ones, and almost all the research institutes, are run by the State Governments. Even in the non-clinical departments of the medical schools, the appointments are made by the local D.M.S. and accepted by the university. The new postgraduate institutes are attached to universities, and the senior jobs in them rank in the academic hierarchy, but here again almost all appointments are made by the local D.M.S. Wherever they may have graduated, the postgraduate students are admitted to the higher degrees of the local university. We had graduates from as far apart as Cambridge and Calcutta. There is nothing corresponding to the diplomas of our Royal Colleges.

The pay of doctors is extremely low, even by local standards. A specialist in his 30s is unlikely to have more than about £300 a year and can get little extra from part-time private practice. A senior professor may get as much as £900 a year without private practice. The retiring age is still 55. Of course, some senior people make large incomes in private, and many distinguished consultants have no hospital appointment. Nursing-homes and private hospitals of all grades flourish. Many of the younger people resign from the hospital service as soon as they have their higher degrees. The diplomas of our Royal Colleges are still very popular, and I am sure will continue to be so, especially as they are the only alternative to the Government's rigid system.

Pay becomes worse the further one goes from the centres, yet it is at the periphery, among the unchanging villages that cannot afford to support doctors, that they are needed most. One is always reading exhortations from elderly politicians to educated young people to go to work in the villages, but they are expected to go about on foot, live in mud huts, cut themselves off from all hope of refresher courses and of promotion, and be content with a pittance. Such dedicated souls exist in India as in all countries, but naturally there are far too few to do what is essential. In obstetrics the position is very bad because far more women than men are being trained Almost all are married, and, though they are able to go on working, they cannot leave their husbands to go to the villages India being a democracy, a member of the hospital service is free to resign, and he will certainly do so rather than be posted to a village He can get better pay abroad, e g , in the U K or Malaya—and so many of the best young people are exported This applies to other fields besides medicine I found that gold-field technicians were still being attracted to South Africa (of all places) by the pay

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[2] Shastri, M. K. *J. Ind. med. Prof.* 1955, 2, 616.

[3] Witts, L. J. *Lancet*, 1957, i, 1343.

THE HOSPITAL AND INSTITUTE

We admitted about forty postgraduates each year, nominated by the medical services of the various States of the Indian Union They had a year's course for a diploma, which almost all obtained, and about half went on for a second year to sit for the Madras M D , which about five obtained The average age of students was rather high at first, but is coming down as people who obtain priority by seniority are passed out As the hospital undertook about 13,000 deliveries and 5000 operations each year, they had plenty of material

Fortunately money had not been lavished to make a show place for distinguished visitors, and we still had the old open airy wards with wide verandahs The poor-class Indian does not understand or like a bed, and so is kept in one only as long as the nurses find it more convenient After this there is a mat on the floor Many of the patients came from long distances, all were poor and mostly illiterate, few received antenatal or postnatal care, and reattendance and follow-up were virtually impossible with our resources Anyone needing long-continued treatment had to be kept in for the whole time, and immediate admission from outpatients was essential Some had been seen by a doctor outside, others had been treated by such people as the local barber's wife, who is the hereditary midwife in an Indian village, while others simply arrived on foot or in a rickshaw and told their tale The number of patients thus has to be, and can be, expanded considerably as required A new building to house laboratories, library, &c , is projected, but fortunately is to be in the old simple style

The average family income of patients was about Rs 40 (£3) per month, and their degree of anæmia and of infestation corresponded The average age at marriage was just over 14 years and at first delivery just under 20 [4] Prolapse was common and severe and also vesicovaginal fistula Much stress is laid on "family planning", but many came for sterility too because it carries grave social disabilities

The patients stood surgery very well despite severe malnutrition and anæmia After a normal delivery the woman would be sent home in forty-eight hours Of course, we saw many specifically tropical conditions—filariasis, malaria, amœbic dysentery—but this hardly affected gynæcological treatments, which differed only in small ways from those seen in the West The medical staff of all grades were most keen and competent Their practice was based on advanced British and American ideas and they easily adapted their Westernised knowledge to the background of their patients Most of the seniors had been abroad for work and study, usually to the U K., U S A , Canada, or Sweden

I found the standard of laboratory medicine good wherever I went in India, but it is confined almost exclusively to academic centres Buildings and equipment are simple—except in a few very favoured places—but adequate I felt that on the whole they had spent the small available funds to good advantage and had avoided frills Biochemistry is largely in the hands of science graduates, but not bacteriology Blood-transfusion is neglected The old-established research institutes continue in being and some new ones have started, especially in the all-important subject of nutrition, but there are still too few and they are hampered by the arbitrary selection of staff Our institute was very research-minded, and the suggested investigations were usually carried out by juniors specially posted by the D M S on request These young people had a very varied background but seemed to tackle the work well under supervision The amount of Indian original work which reaches print seems to be very small compared with the effort put into it, but it is hard to see just why this should be so

The best technicians in our sense of the term are junior science graduates, classified as "assistants" Lower grades are not well trained, and indeed most ancillary staff are of poor quality because deliberate policy keeps the number of jobs high and the pay low This may still be necessary in India, but the Western visitor becomes irritated by the rows of peons asleep on benches and of clerks who cannot type accurately Many of the routine chores are done by junior medical staff who stay too short a time at them to become skilled

Of nursing I was unable to judge, but I understand from visiting experts, and from those who have been under their care, that Indian nurses can be described as moderate They are kind and attentive, but most are lacking in advanced techniques Their pay and conditions of service are relatively rather worse than those of doctors Many more are needed urgently, especially midwives

The main object of the institute was, of course, teaching, and for this we had adequate facilities, firstly in the flood of material, secondly in the quality of the teachers, and thirdly in the equipment Much of the teaching was informal, but seminars and lectures were held We had a cool lecture room, projectors, tape recorders, and good photographic equipment, with a trained "photo-artist" who also assisted students to prepare their "books" of cases—an examination requirement obviously based on that for the M R C O G We had a small museum which we recatalogued and enlarged We took a fair number of the world's journals relevant to the work, but there had not been time to build up a library We all relied heavily on the library of the British Council, which has a very good and up-to-date medical section, containing many of the summaries of recent work which are so useful to postgraduate students Indeed the British Council is very active and influential in India

Unfortunately necropsies were almost impossible to obtain Junior doctors shrink from asking for them, but the seniors have even attempted to introduce legislation to facilitate them I had not realised how important they are until I was without them

GENERAL BACKGROUND

Social

Working with enlightened and friendly colleagues and students, it was often difficult to remember how different was their background from my own, but we must do this if we are to understand their problems and especially if we are to help Indians who come to this country and are uprooted from their own culture

The ancient organisation of caste and family was described once and for all by Dubois,[5] and the account has been brought up to date by Thomas.[6] Some recent writers, such as Carstairs,[7] have implied that it is now confined to a small section of the people, but, in South India at any rate, it is still almost universally valid, although in the cities there is little evidence of it to the casual observer. The great majority still live in the old way, all the sons, with their wives and children, remain under their father's roof, the wives do not speak to their husbands in the presence of their mother-in-law, and marriages are arranged by the parents. Unless destined to go to a university, girls in enlightened families are still married off at the minimum legal age of 16, while in poorer and more backward families this minimum is generally disregarded. Like so much recent legislation apparently directed against ancient wrongs, that against child marriages is so worded as to be easily disregarded in practice.[6] Despite forecasts to the contrary (e.g., Wheeler[8]) this way of life has probably become more rigid since independence. The various "communities" do not mix with each other in their own homes, and I am sure that this—not European standoffishness[9]—is why mixing between Indians and Europeans has always been so difficult. Outside their homes, mixing is now general in the cities.

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[4] Rewell, R E *J Obstet Gynæc Brit Emp* 1957, 64, 821

[5] Dubois, J A Hindu Manners Customs and Ceremonies (revised by H K Beauchamp) *London* 1906

Economic

India is an overcrowded country with an impoverished soil and few industries as yet. The cow is sacred: innumerable semistarved brutes crop all the young vegetation, producing very little milk, and lack of wood leads to their dung being used as fuel instead of as manure. The only animal protein that many people will take is curd made from the milk of cow or buffalo, but its scarcity makes this expensive. Meanwhile the population increases.

India then must industrialise, and faces the now familiar problem of how to do this rapidly without inflation and profound social dislocation. Medicine cannot claim an undue slice of increased productivity, but, without disparaging what has been achieved recently, I am sure that much more could be made of the resources available. The methods of administration are extremely wasteful, and in any case it is an insult to responsible, trained, and honest people to tie them up with red tape as is done. This treatment has to be experienced to be believed. Doctors in hospital must be allowed much more say in nonclinical and administrative matters than at present, they should also have some security of tenure in senior posts, and better methods of promotion must be devised. With the present expectation of life the retiring age should be raised to 60: by preventing waste of skill this would save money. Most important of all, the periphery must be made attractive. It is there that the real work is to be done, and it is there that at present nobody will go if he can possibly avoid it. On the practical side medicine is keeping up well, and fortunately practitioners are striving to maintain a place well in the mid-stream of present-day medical thought. To continue the use of English will certainly help to keep them there. (The only subject in which no regard was paid to accepted opinions appeared to be fæcal hygiene.)

NEED FOR HELP

India remains a poor country and needs help to raise herself. Western experts are welcomed, and every facility was given me by the people with whom I was actually working, the atmosphere was most friendly and I soon felt myself to be one of the team. In spite of the shortage of trained people, there is no room in India now for the European doctor to settle. Indians intend to keep their own jobs for themselves and cannot understand how we in Britain admit people from other Commonwealth countries or European refugees. But organisations like the Colombo Plan allow British doctors to give their help for a time, without personal loss and indeed with gain in many ways.

I am extremely glad that I went to Madras. The officials of the Commonwealth Relations Office, both in the U.K. and in India, were most helpful, and my pay and conditions of service were very good. Pay is very important, because a high standard of living is necessary for us to maintain efficiency in a difficult climate. My conditions certainly were very much better than those of people whom I met working for the World Health Organisation.

Conferences

WORLD FEDERATION FOR MENTAL HEALTH

THE 11th annual meeting of the Federation, held in Vienna from Aug. 24 to 29, had nearly 500 participants from 34 countries. Its main theme was uprooting and resettlement.

Dr BROCK CHISHOLM (Canada), the president, in an address called Man's Responsibility in the World, spoke of the continued existing of second, third, and perhaps fifth class citizens, who are deprived of certain rights, and of the ridiculous people who still judge by such signs as colour of skin. There are very few communities without some degree of discrimination. Describing the way in which children are being prejudiced in early life, he recognised five abilities as necessary for the assumption of responsibility in the world today:

1. The ability to face and accept facts and act upon them.
2. The ability freely to change attitudes independently of parents and forbears, and without guilt and anxiety.
3. The ability to live without discrimination and prejudice.
4. The ability to love without discrimination and prejudice.
5. The ability to make discoveries, and to appreciate what is discovered.

He drew attention to the pitifully small proportion of research effort that is devoted to mental health and to human behaviour.

Refugees and Immigrants

Dr MARIA PFISTER (W.H.O.), discussing Resettlement as a Sociological Problem, pointed out that the more coercive the conditions in which resettlement takes place, the stronger the regression in the behaviour of both parties, and that in periods of crisis this will bring out stress that is only latent at other times. Another very important factor is the degree of uniformity or diversity of the social ideal held by the two parties.

She came to the general conclusion that, whenever possible, there should be a phase of planning and preparation for migration for both parties. In any resettlement there must be a "catalysing" team which is briefed with knowledge of the factors influencing both parties, and it should be constantly asked, "how does one resettle?" Mass action is the arch-enemy of mental health in resettlement. Families must be sent as single units, and there must be no separation of children from parents. In all resettlement processes there is a great need for time, and this is a need which few Europeans know instinctively.

Mr ELFAN REES (World Council of Churches) gave some impressive facts about the 40 million people driven from their homes since the close of the second world war. They form a third force in society—the proletariat of the dispossessed. He reminded the meeting that, besides a

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6. Thomas, P. Hindu Religion, Manners and Customs. Bombay, 1956.
7. Carstairs, G. M. *Lancet* 1955, i, 1217.
8. Wheeler, M. Still Digging. London, 1955.
9. Toynbee, A. J. A Study of History (abridged by D. C. Somervell), vol. 9. London, 1957.

camp psychosis, there is an out-of-camp psychosis—the attitude of refugees who do not want to leave a camp

Prof Erik H Erikson (U S A) spoke of the normal identity crises—for example, during adolescence or in any major change of status, or during involution Just as normal people will react differently to these identity crises, so will refugees There is a positive side to the refugee position, in that a person who has never felt uprooted may never have had a strong positive sense of being at home If he has never been isolated, he may never have found an identity To become an alien may for some people be to become mature

Dr H Strotzka (Austria) outlined the work of the Austrian Society for Mental Hygiene in establishing teams to tackle the mental-health problems of the 183,000 refugees passing through Austria Counselling services and other medical attention was available in such a way that, though there was much disturbed behaviour, no refugee was sent to a mental hospital It was seen that such admission would hopelessly compromise the future of the individual refugee From experience Dr Strotzka emphasised the terrible effects of lack of information and communication, in spreading mistrust and paranoid attitudes

Prof Dan L Adler (U S A) described the Psychological Problems of the Voluntary Migrant to Australia

A study of the response patterns of more than 400 immigrants of various nationalities was made, and compared with over 200 Australian children's responses This showed how the various patterns of family behaviour, such as the mother's or the father's autonomous behaviour, tended to approximate to the general Australian pattern, from quite diverse original patterns, within about six years Also, it seems possible to interpret parental dissension as an index of general tension The main hope of the Australians in respect of the refugees is in the children rather than in the existing families

Prof John C Sawatsky (Canada) talked about the settlement of 400,000 immigrants in the metropolitan Toronto community, where they now form almost a third of the population Favourable conditions allow the immigrant families to make a simple transition, but it is for the children to complete this process

Dr Kenneth Soddy (scientific director of the Federation) summarised the reports of the 13 discussion groups on various aspects of the refugee situation, the film discussion group, and the special conference of immigration officials which was held alongside the main meeting This conference was attended by senior health and welfare officials of the main countries with extensive immigration programmes This informal conference of Governmental representatives made a number of recommendations for the improved handling of refugee programmes

Prof Hans Hoff (Austria), president of the Federation for 1958–59, gave an address on Home and Identity, in which he spoke of the importance of landscape, history, and past experience on the future happiness of migrants, and the need to take account of these factors and apply them scientifically

Past and Future

The first Dr Mary Hemingway Rees memorial lecture was given by Dr H V Dicks (London), on Mental Health in the Light of Ancient Wisdom All the great ancient religions, he said, want man to be happy, good, and free, and they all agree on the threefold need for adjustment, self-realisation, and integration This is part of the aspiration of mental-health work

At the general session, Dr J R Rees, director of the Federation, outlined some of the plans for an intensive programme of international work for the World Mental Health Year, with five main themes

1 The needs of children (the family in a changing world)
2 National surveys in the field of mental health and ill health
3 Teaching about mental health (professional people and other workers)
4 Mental health aspects of industrial change (human relations in industry)
5 Psychological aspects of migration

EUROPEAN LEAGUE FOR MENTAL HEALTH

On Aug 23 the European League met in Vienna under the presidency of Prof Hans Hoff

The Older Worker and Retirement

Dr Doris Odlum (London), immediate past president, opened a discussion on mental health problems of the older worker and of retirement She pointed out that nowadays more people retain much of their vigour and working capacity until the late 60s or even later, but on the other hand many people even in the 50s cannot get suitable employment and some are arbitrarily retired long before their capacity for efficient work has diminished The result is not only a serious loss of man-power but also, often, considerable disturbance of mental health

Few people give up work voluntarily merely because they want more leisure in fact, many dread the prospect of idleness, they feel discarded and lose their incentive, which can lead to *premature deterioration Unlike older women with homes and* husbands and perhaps grandchildren to care for, the retired man may not be wanted in the home or indeed anywhere In the case of widows, or widowers, or the unmarried, loneliness is often one of the greatest problems

The preventive and remedial measures which Dr Odlum discussed include the provision of more suitable work, part-time work, and the avoidance of compulsory retirement as far as possible Employers, local authorities, and voluntary agencies could do much to prepare people for retirement, to provide activities and interests, and to maintain social contacts

The problems seem to be similar in all industrialised communities and especially in countries which are being rapidly industrialised The pattern of living is changing too quickly for older people to adapt themselves, also the situation is less favourable to them than that of an agricultural community

Prof Paul Reiter (Copenhagen) said that it is now realised that many cases thought to be senile psychoses are really psychogenic and can be greatly helped by medical and social care

Dr André Repond (Switzerland) remarked that the problems of the agricultural communities are considerable and not to be ignored Their pattern of life, too, is changing He wondered whether the *old are* unhappy Have we any real knowledge? If they are, what is the basis of their unhappiness? Perhaps it relates rather to their earlier frustrations and emotional conflicts than to the present

Dr Claude Veil (France) pointed out that preparation for ageing really begins in childhood and at school The lower the standard of education and cultural background, the earlier the decline of mental powers He agreed that men would benefit from learning household arts and activities *as children Some people seem never to be at the right age* it is either "you are too young", or "you are too old"

Dr Socken (West Berlin) said that people who have a religious background or a feeling of purpose adapt much more happily to increasing age

ISRAEL MEDICAL ASSOCIATION

THE fourth World Assembly of the Israel Medical Association was held in Tel Aviv on Aug 12–24 The assembly is now a triennial event, and this year it coincided with the celebration of the tenth anniversary of the State of Israel.

Prof **HERMAN ZONDEK**, honorary chairman of the conference, remarked that scientific thought had been largely dominated by the mechanistic doctrine of causality, but, despite much progress, the riddle of life had not been solved The physician in our time was called on to take a greater part in public life than hitherto, particularly in his contribution to education "The younger generation, drunk with the progress of technology, looks upon an empty soulless world Humanity in our time is sick, suffering from numerous endogenous ailments of moral, political, and economic kinds, and from extraneous threats to its very existence, the most dangerous of them the unchaining of atomic power Humanity will with difficulty get rid of this threat, it seems easy to die with the atomic bomb, but how shall we live with it?"

Public Health

Dr S **BYESH**, director-general of the Israeli Ministry of Health, said that the health of the Jewish population of Palestine in 1948 was fairly good. With immigration were introduced many carriers of disease and susceptible persons The lower standard of living, the lack of proper housing, and the ignorance of the immigrants in matters of hygiene resulted in deterioration of the health of the people, culminating in an increase in infant-mortality and crude death-rate, and in the spread of tuberculosis, poliomyelitis, and malaria

Intensive health measures had resulted in effective control of most of these conditions, and at the end of the ten-year period the health conditions of the country compared favourably with those in the U S A and most European countries

There was 1 doctor to about 450 inhabitants, and there were about 3 general-hospital beds to 1000 inhabitants

Prof G G **MER** said that malaria in Israel is dying out The present low incidence had been accomplished by control of anopheles breeding, the use of residual insecticides, and efficient medical services The occurrence of a few scattered cases pointed to the presence of human carriers in the country Because in the neighbouring countries, too, intensive anti-malaria work was being carried out, the complete eradication of malaria in Israel could be regarded as a certainty, provided immigration of malaria carriers could be prevented and the present number of carriers could be reduced

Serum-lipids

DR. D **BRUNER** said that the population was now composed of, on the one hand, European Jews, among whom there was a high incidence of coronary-artery disease in middle age, and, on the other hand, Yemenite Jews, who were practically free from atherosclerotic heart-disease in middle age Of 32 Yemenite farmers who had been investigated, none had had a level of β-cholesterol over 180 mg per 100 ml , and 27% of the total cholesterol was bound to the α-globulins In this group the percentage of α-cholesterol was nearly double that in a group of patients with ischæmic heart-disease and a third higher than that in healthy European Jews

Mediterranean Fever

Dr H **HELLER**, Dr E **SOHAR**, and Dr L **SHERF** reported that the great majority of patients with familial Mediterranean fever were non-European Jews, and the second large group consisted of Armenians The disease began in childhood or early adolescence and persisted for many years It was characterised by recurrent attacks of fever accompanied by abdominal pain, arthralgia, chest pain, and sometimes skin manifestations The attacks were brief, usually lasting for twelve to forty-eight hours, and recurred at irregular intervals During the abdominal attacks signs of peritoneal irritation usually appeared In X-rays of the abdomen fluid levels were found in the intestinal loops A small transient pleural effusion might be detected in chest films Joint pains might be restricted to one joint or might attack several at a time, sometimes the affected joint was warm, red, and swollen, and fluid might be found in the synovial sac, joint manifestations usually declined more slowly than the others Between the attacks the patients were well The disease terminated, in some cases, in renal failure and death due to amyloidosis Extensive laboratory investigations had revealed very high erythrocyte-sedimentation rates, high fibrinogen levels, and slight spherocytosis In many cases proteinuria was found as well Therapeutic measures were of no avail No patient ever recovered, but remissions did occur During pregnancy complete remission was usual The clinical picture, as well as the familial incidence and the limitation of the disease to certain ethnic groups, suggested that the cause was an inborn error of metabolism

Pneumoconiosis

Dr E E **LIEBER** (Great Britain) described an inquiry into whether the dust and vapours from various chemical substances could cause chest disease He pointed out the importance of medical and radiographic examination of affected persons and of skin-sensitivity tests The substances involved included (a) dusts (such as glass monofilaments from the cutting and handling of mats, cloths, rovings, and beryllium-copper alloy, fine-glass and epoxy-resin dust, and polyester dust) and (b) vapours (styrene from resin compounding and mixing, and methylethylketone peroxide accelerator) In some patients who came under his care there was a reduction in vital capacity, and chest radiographs showed occasional lung markings and sometimes emphysema The prognosis in all cases was excellent. The patient's condition did not continue to deteriorate after removal from exposure, and this dust disease might be described as a "benign pneumoconiosis" Dust-extraction equipment and the usual additional prophylactic measures protected workers engaged in handling glass fibres and epoxy resins

Dehydration

Dr M **TOOR** said that workers in the Dead Sea region in the summer drank 5 5–10 litres a day Despite this intake, outdoor workers showed signs of dehydration, manifested by weight loss, hypernatræmia, slight metabolic acidosis, and relative hyperchloruria The daily urinary output was in some as low as 300 ml Hyperventilation, present at rest, increased after work The sodium-potassium ratio in the saliva decreased after work In order to determine the influence of varying water intake, 10 fully acclimatised subjects had been examined after they had walked for two hours at 6 km per hour The outdoor temperature was 42°C They were divided into three groups (*a*) without fluid intake, (*b*) without limitation of fluid intake, (*c*) with forced fluid intake The group without fluid intake had shown an average rise in body temperature of 1 9°C and an average drop in body-weight of 1225 g per hour The glomerular filtration-rate was low and little urine was excreted, the alkali reserve remained unchanged, but the pH dropped slightly The group which drank according to inclination lost 400 g body-weight per hour, and the average body-temperature increased by 0 7°C The group with forced water intake drank nearly 2 litres per hour and gained 500 g per hour in weight, body temperature remained constant Their perspiration did not increase in direct ratio to the water intake, but the glomerular filtration-rate, the amount of urine, and the urinary sodium increased. The alkali reserve dropped, but blood pH did not change This experiment indicated that fluid intake according to thirst urge was not sufficient, on the other hand, positive water balance could prevent disturbances in homœostasis even in the hot climate of the Dead Sea region

Before Our Time

ALFRED RUSSEL WALLACE
(1823-1913)

AT school I was given as a prize Wallace's *Travels on the Amazon and Rio Negro* I remember being puzzled when I read on the title-page the author's claim to be the co-discoverer with Darwin of the theory of the Origin of Species I had heard a great deal about Darwin but Wallace's name was new to me Many people must have been equally puzzled on reading the centenary articles which have recently appeared, for most of these, while starting off with the presentation of the two independent papers by Darwin and by Wallace to the Linnean Society on July 1, 1858, thereafter refer only to Darwinism Some account of Wallace and his relationship with Darwinism may therefore not be out of place

Alfred Russel Wallace was born at Usk, Monmouthshire, his father being nominally a solicitor but actually a lifelong idler Leaving school at the age of 16 he became a land surveyor and architect and later a schoolmaster He early became interested in botany, and a chance meeting with H W Bates extended his interest to entomology and in due course led him to spend four years on the Amazon (1848–52) On the voyage home the ship was completely destroyed by fire and most of his collection was lost In 1854 he went to Malaya, where he spent eight years in exploration and in pondering over the problem of evolution In the idea of evolution itself there was nothing new It had been adumbrated by Goethe (some people find suggestions of it in Empedocles and Ovid) and developed by Lamarck, and it was now engaging the attention of many thinkers, among them Herbert Spencer, Robert Chambers, and Sir Charles Lyell The unsolved problem was the cause of evolution

In February, 1858, while recovering from an attack of ague at Ternate in the Moluccas, Wallace suddenly recollected Malthus's *Essay on Population* which he had read twelve years previously and he at once realised that this gave him the key which he sought " There suddenly flashed upon me," he wrote, " the *idea* of the survival of the fittest " He hurriedly wrote out his theory and sent it to Darwin Darwin, also inspired by Malthus, had for many years been accumulating evidence on similar lines Lyell, evidently realising from his wider experience that a fundamental generalisation was imminent, had been urging him to publish his results lest he be forestalled Darwin, however, was in no hurry

On receiving Wallace's communication (the author being unknown to him) Darwin was dumbfounded " I never saw a more striking coincidence," he wrote to Lyell " If Wallace had my MS sketch written out in 1842, he could not have made a better short abstract Even his terms now stand as the heads of my chapters " On the advice of Lyell and Sir Joseph Hooker, Wallace's essay and an abstract of Darwin's conclusions were jointly read Though they were in general agreement, the views differed in certain respects In particular, Wallace early abandoned the Lamarckian doctrine of the inheritance of acquired characters, but Darwin adhered to it for the whole of his life, putting forward his complicated pangenesis theory in explanation

The simultaneous appearance from two sources of a revelation which shook the scientific and religious worlds might well have had unpleasant consequences But the very reverse happened So far from indulging in jealousy and acrimony, Darwin and Wallace became lifelong friends with the warmest mutual regard On the authorship of the theory they vied with each other in deference "You ought not," wrote Darwin, "to speak of the theory as mine, it is just as much yours as mine" To this Wallace replied " As to the theory of natural selection itself I shall always maintain it to be actually yours and yours only " This he certainly did, for in all his writings he called the theory " Darwinism "

On his return from Malaya Wallace began to write voluminously The most important of his biological books are *The Malay Archipelago, The Geographical Distribution of Animals* (which became a standard work), *Tropical Nature, Australasia,* and *Island Life* In *The Wonderful Century* he displays his interest in physics, chemistry, astronomy, geology, and cosmology

Unlike Darwin, who confined his activities to science, Wallace was interested in everything that concerned human welfare

At an early age he was attracted to Robert Owen's New Lanark experiment and later he was influenced by Herbert Spencer's *Social Statics* After many years' hesitation he became a socialist, numbering among his friends the leading socialists of the day He trenchantly poured out his views on capitalism, wages, poverty, and militarism To the emancipation of women he attached a peculiar biological significance, linking it up with the theory of natural selection He was convinced that if women became economically and socially independent they would select their mates with more discretion, so that " numbers of the worst men among all classes who now readily obtain wives *will be almost universally rejected* " He summarised his sociological views in *The Revolt of Democracy* and *Social Environment and Moral Progress*, both written in his 90th year

His special interest, however, was the nationalisation of land, a subject on which he felt that his early experience as a surveyor enabled him to speak with authority When, in 1881, as the result of an article which he had written in *The Contemporary Review*, the Land Nationalisation Society was formed he became its president and he retained the post until his death

Like so many intellectuals he was singularly naïve in medical matters

In *My Life* he relates how he was cured of asthma by living almost entirely on beef with small quantities of bread or vegetables, fruit, eggs, and light milk puddings This regimen he learnt through a friend from an American doctor named Salisbury who claimed to have proved that asthma, palpitations, gout, rheumatism, and other disorders were due to malnutrition caused by interference with digestion and assimilation through the excessive consumption of starch Wallace lapped all this up " Dr Salisbury ", he wrote, " has found for the first time in the history of medicine, a *cure*—not merely a *palliation*—for these painful and distressing maladies " He did not, however, propagate this opinion

More important is his violent opposition to vaccination In *Forty-five Years of Registration Statistics* and again in *The Wonderful Century* he claims to prove from the Registrar General's figures and other sources that vaccination, so far from preventing smallpox, actually increased susceptibility to it It was " a gross interference with personal liberty and the sanctity of the home It was utterly opposed to the teaching of sanitary science and one of those terrible blunders which, in their far-reaching evil consequences, are worse than the greatest of crimes "

While he was a schoolmaster he became interested in mesmerism, phrenology, and phreno-mesmerism, the last-named being a procedure whereby certain " faculties " were elicited in the mesmerised person by touching with the finger the part of his head indicated by phrenological teaching From this Wallace was led to spiritualism of which he became one of the most prominent advocates, regarding it as the greatest discovery of the century, surpassing even his own discovery of natural selection

In *Miracles and Modern Spiritualism* he gives a detailed account of the phenomena including those which he himself witnessed in this country and America Spiritualism was, in his opinion, superior to revealed religion " After death man's spirit survives in an ethereal body, gifted with new powers, but mentally and morally the same individual as when clothed in flesh " He enters upon an endless progression, the rapidity of which depends upon the extent to which he used his faculties while on earth Spiritualism thus provided a stimulus to moral behaviour during terrestrial existence Wallace was always careful to describe the phenomena as " preternatural " rather than " supernatural " His friends might scoff, but at least he was in the good company of Sir William Crookes and Sir Oliver Lodge

Financially, Wallace fell on evil days His income from his numerous books and lectures was surprisingly small and was reduced by injudicious investments and by the defalcation of a builder But this was not the worst In 1870 he accepted a wager by a certain John Hampden to prove that the surface of inland water was curved The experiment took place on the Bedford Level in the Fens, with the editor of *The Field* as arbiter and stakeholder Though Wallace was pronounced the winner his adversary, despite his felicitous name, defaulted, taking advantage of a legal quibble and making himself a bankrupt Unsubdued, moreover, by four prosecutions for libel and a term of imprisonment Hampden persecuted poor Wallace with the most scurrilous abuse for fifteen years Legal costs and the expense of the experiment reduced Wallace's finances to the lowest ebb In 1881, Darwin and Huxley persuaded Mr Gladstone to grant him a Civil List pension of £200 a year He died in his 91st year, his mind and pen active to the last Among the honours he received were the Order of Merit, the Royal medal and the first Darwin medal of the Royal Society, the hon LL D of Dublin University, and the hon D C L of Oxford University

Fearless and uncompromising, Wallace never minced his words The Joint-Stock Companies, he declared, swindled and plundered the public, the whole commercial fabric of the country was permeated with dishonesty, gambling, and robbery, while the administration of justice was thoroughly immoral He castigated scientific orthodoxy and was never so happy as when propounding or defending an unpopular thesis As may be imagined, his critical faculty often deserted him and he lacked a sense of proportion He was, for instance, ready to believe that spiritualists in the United States numbered 8–11 million, not stopping to reflect that this meant more than half the then existing adult population Though he did not believe in Christianity he was a confirmed deist He held that life could be explained only by postulating a Life Principle which implied a Creative Power, a Directive Mind, and an Ultimate Purpose which was the Development of Man, " the one crowning product of the whole cosmic process of development "

FFRANGCON ROBERTS

In England Now

A Running Commentary by Peripatetic Correspondents

MY work is full of meaning—or at least I mean it to be The only trouble is that I just can't see what it means Hints in plenty oh yes! But I can't get the meaning of them *Pro*meanings that's what they are, they only need activating Perhaps that's the trouble, my brain is deficient in promeaning*ase* it won't activate Or, half a minute it might be worse, suppose it's not just a deficiency state perhaps it's a toxic condition, perhaps my mind actively secretes an *anti*promeaningase How to neutralise this? Can it be bound to plasma-protein and taken to the liver for detoxication? *Degrado*antipromeaningase? What's that? Needs a co-factor? *co*-degradoantipromeaningase? Now we're getting somewhere I can almost see what it means

No! the pattern's lost again The nascent meaning showed a strong selective affinity for *anti*-meaning which converted it rapidly to inactive *meta*-meaning But that's what it all means! Promeaningase and anti-meaning are clearly in excess and therefore constant, so that we have a system of effective first-order consecutive reactions

promeaning→meaning→metameaning

and—oh but look how ghastly! This means that meaning has only a fleeting ephemeral existence after all I really do call that pretty mean, don't you?

* * *

Drinka Pinta Milka Day? You'll be lucky Our village has been shaken from taproom to shippon Joe Moffat has been booked for obstructing the highway Not, mark you, with the old green van that has the mudguards tied with binder twine, not even with the shiny new tractor We could have forgiven the Law for that Joe spends a lot of time in the Plough on market day No, it was far worse, he was run in for blocking the road with his milk cows It would never have happened in the old days P C Grimble would have got off his bike and helped to turn the herd in at the gate But not those new motor patrol chaps from the town they focused their radar on the backside of Buttercup and timed how long she took for two furlongs Joe got fined a pound and had to listen to a sermon on how to fit sixteen cows into the *Highway Code*

I feel very heavy-hearted about the whole affair The rolling English milk cow made the rolling English road There is some elemental simplicity about waiting for cows to move on Quite a different mood from fretting behind 100 tons of steel boiler or a surrealist aircraft fuselage on the trunk road All our motorists are fully conditioned to lowing herds winding slowly o'er the lea, even if they are not quite sure what is a lea It would be vulgar impatience to expect a cow to trot single-mindedly from grazing ground to milking parlour, and it would cost a lot more from the public purse to mow the grass verges No, there is something very soothing in slipping the clutch gently behind a herd of cows Those extraordinary pelvic bones protrude like the tail fins of a modern car how curiously pudendal have become the rear lights of Luton. One could muse on about following cows and cars, keeping a decent interval from the one in front But cars go on like that for hours all the way to Brighton ten minutes and two furlongs can pass a lot of cows

Of course, Joe knows my car If he thinks I ought to be off to an urgent case, he turns the herd with the dog, but that is not often Most days he just jogs alongside the open window, talking of life and country things, and poking incredibly unhygienic fingers into his mouth to whistle commands to Moss The herd really do not need a cow dog they have strolled the road for years And when they have turned in off the tarmac, Joe and I lean over the top bar of the gate and put the world aright Alas, those happy days seem gone A resolute tractor-mounted Moffat will have to punch his cows in the derestricted stampede of death on our roads Sixteen udders will sway in the churning rush, sixteen cuds will turn sour

All that will be left for us to say to you will be Eata Nounca Cheesa Day.

• • •

Each year at this season our city undergoes the ordeal of a festival of music and drama, and the hounds of culture can be heard baying in every close and wynd of the Old Town. But it is refreshing to be reminded that culture is not a prerogative of any particular income-group or intellectual coterie.

Yesterday I had to decline the offer of a game of golf with a senior colleague (a celebrated physician) because I was going to *Tristan and Isolde*. He was aghast. "What! Pay £2 and sit for five hours listening to all these Germans screaming away?"

This morning, at an autopsy on one of my patients, the mortuary porter kindly inquired if I had enjoyed *Tristan*, and added: "I've seen it twice, Wagner is very good, but give me Verdi every time."

• • •

On the coach on the way back I happened to be sitting next to him. His eyes were still alight with the fire of battle. "We will have them at the hospital," he said. We had been on our annual trip to the sea and our Administrator had spent the whole time on the dodgems. With his usual single-mindedness and determination, he had hurled his car against all comers, with dexterity and speed he had bashed and rocketed all other cars off their course. "The hospital will run on wheels," he exclaimed. "We will have them in the corridors and have dodgem parks outside each ward, at the front door, and all centres of activity. We shall have to ban all pedestrians. You can each have your own car," he continued generously. "We will give Matron and the sisters one each. We will have dodgem cars, dodgem stretchers and dodgem wagons for the stores. They won't be noisy, all electric, fixed with silencers. It will be quieter than it is at present. Of course we will have to have one-way traffic so there will be no bumping," he continued regretfully. "We might have an occasional Bump Day though," he added musingly. "Think of the time it will save. No more walking through miles of corridors." I imagined the Chief's round hurtling off from the front door to the back block and groaned to myself. "It will all stop at the ward doors," he said. "Of course, we shall have to cut them out on visiting days," he pondered, "the patients see little enough of their visitors already with television being on. . . ." I didn't listen any more. He was still talking rapidly. I fell asleep.

I think he really means to go through with it. Workmen have appeared in the corridors and a wire mesh is beginning to cover the ceilings.

• • •

Sophistication in the treatment of myocardial infarction is unbounded. After three days of frightening arrhythmias, electrolyte manipulation, and norepinephrine, my friend was well enough to state his own ideas on treatment. "Not by electrolytes alone" was his philosophy. So his wife and I, and a most enlightened hospital administration, have prevailed on a well-known string quartet in this mid-Western city to play for him. Every afternoon they trundle in, and they are at present wading through the Beethoven quartets. We persuaded them that atonal music might play havoc with his rhythm.

My friend's room is a very popular place these days. And his heart? Beating away in perfect time.

• • •

In that part of Yorkshire which will eventually comprise the South Riding it is an ignoramus indeed who is not aware of the St. Leger and of Race Week. At this time "failed attendances" in the outpatient departments may approach 50% of the total appointments, and those who do attend are in their Sunday best and apologise for troubling the doctor at such a time. Non-racing newcomers who fail to make note of this *jour de fete* may sooner or later find themselves at a disadvantage in the surgery; for in later months medical histories will include perhaps a cough which began "happen the month before race-week" or a pain which was previously experienced "the year Lupus came in first."

Letters to the Editor

EDUCATION FOR THE TROPICS

SIR,—I hope there will be a burst of applause, from spectators and players alike, for Mr. Wright's plea (Aug. 30) that education should take account of medicine in the tropics: a crescendo of delighted drumming would be more appropriate than polite handclaps from the pavilion.

In East Africa, to continue Mr. Wright's sporting simile, the game is much the same as in West Africa, though the pitch may be a little different. My strongest recollection is of rural dispensaries, of which in Uganda there are about 10 for every hospital, where the game may be at its simplest but the players are just as much in earnest. Here attends a third of the population annually,[1] and probably nearly *every* baby in its first year,[2] all to be seen by locally trained medical auxiliaries: there may be a small ward with a few beds, and the most powerful weapon is penicillin.

Common sense suggests that the rules of this game also should be taught—how to integrate these rural units with the hospital service, how best to make use of the times the doctor can visit them, what part they can play in prevention of disease, how much can be expected from the medical auxiliaries. Examples showing how other underdoctored countries have made use of such institutions would prepare students for this aspect of medicine in the tropics.

The educational, the social, and the preventive aspects of medicine are, as Mr. Wright so clearly argues, all-important in areas where there is so little background of health education, societies are so different from English, and successful prevention can reap such encouraging rewards. It is in these fields that physical *example* can play such a large part. To take a bad example, it is our own emphasis on "the *microscope*, the pill, *and the injection*" *that has evoked such a demand* for them from the local populations, and now the demand is often used as an argument for persisting with this disastrous imbalance (in Uganda, overall mortality under 14 years of age is 400 per 1000[3]). Another bad example has followed where no good example has been given: mothers are aware of the dangers of malnutrition, and therefore buy the imported baby-foods on which Europeans feed their children, but they can neither read the instructions nor afford enough—with the tragic result that malnutrition is aggravated. An encouraging response has followed the example afforded by a gift of skim milk powder from the Church World Service of the U.S.A.: in the child welfare clinics where this has been given away, attendance has doubled in the past two months. If the experience of other countries is repeated, the knowledge of the benefits of good nutrition will remain even when the gift has come to an end: the misfortune is that there are only a score or so regular child welfare clinics in Uganda at present—although there are about 900,000 children under 5 years of age.

One point to which I think Mr. Wright might have drawn more attention is that in the tropics the majority of doctors—certainly most of those associated with the kind of medicine he describes—are in the Government service. Now it is a strange paradox that under these conditions the fewer the doctors the less medicine (either preventive or curative) they seem to practise. Although surrounded by a fascinating variety of medical conditions, and in their monthly records accumulating figures of the greatest value for a public-health policy, the only figures which many are allowed to take an interest in are those of numbers of blankets or amounts on payrolls. In tropical Parkinsonism, office work expands to the exclusion of medicine.

Mr. Wright calls for "rural medical officers equipped with the necessary imagination and energy" and feels that the "centralised administration" has little part to play, and on this premise he builds his hopes for the value of better education for those going to the tropics. But in fact the administration has an all-important part to play. Medical officers, like other human beings, tend to concentrate on what their superiors show an interest in: if the director puts foremost the many aspects of medicine in the tropics, the M.O. will do likewise; if he puts foremost accounting, storekeeping, and administration, so will the M.O. The problem is how to ensure that the directors have the right outlook, and this, I feel, is beyond the scope of education.

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[1] Report of the Medical Department of Uganda for the year 1956. Entebbe.

[2] Based on monthly returns from rural dispensaries, 1956.

[3] Martin, C. J. *Population Studies*, 1953, 7, 181.

London, W.C.1 **JOHN MCFIE**

BREAKING UP THE MENTAL HOSPITAL

SIR,—While applauding Dr. Baker's application of methods of combating institutionalisation, I think that several of his propositions (Aug. 2) require scrutiny.

Banstead Hospital, he says, now has 450 patients less than three years ago. Most mental hospitals have about 10% of their population on leave at any time, and if it were decided to discharge patients instead of sending them on leave their population would drop, but this is not necessarily a good thing. Dr. Baker does not tell us how many of the discharged patients have found their way into other mental hospitals or have committed suicide.

Banstead has a catchment area which includes parts of Westminster, Chelsea, and Battersea; the population is mobile, and it is reasonable to suppose that more discharged patients would move out of the area than into it. Furthermore several other hospitals take patients from the catchment area of Banstead, and some doctors would prefer to send patients to these because they do not agree that a voluntary patient should be required, *before admission*, to sign a form giving permission for electroconvulsion therapy, insulin, and any other treatment considered necessary.

The 40% rise in admissions given may include readmissions. It is not clear to me whether in the past many of these "admissions" would have returned to hospital during a period of leave.

Apart from the possible speciousness of statistics, a very important question arises if one looks at the effect of rapid discharge on the patient and community. Has investigation been made of the distress caused to the patient, his family, and others? Can Dr. Baker reassure me that in breaking up the mental hospital he is not breaking up the home? I wholeheartedly agree that businesslike methods are desirable in mental hospitals, but, whereas a business man takes the consequences of his decisions, the psychiatrist makes decisions which do not affect him: it is the patient and his family who take the consequences. There is a danger that the public may be made less tolerant to mental disease by having it thrust among them before adequate aftercare services are provided, and this in turn may hamper the development of these services.

I think it is generally agreed that a neurosis characterised by apathy, submissiveness, and loss of individuality results from factors arising in an institution. It is only in the past few years that this neurosis has been realised to have an ætiology separate from the mental disorder causing admission.[1] From visits to other hospitals and reading, it is my impression that many hospitals have introduced, and are introducing, programmes to stop causing this disorder and to cure it where it has been produced. Dr. Baker may think that dividing a large hospital into smaller units is a solution, but when examining this contention one should remember that hospitals built on the villa system with units of 30–50 patients also produced institutional neurosis in quantity and degree much the same as the hospitals with "barn-like wards" built in the Victorian era.

To say that the provision of hostel accommodation and sheltered workshops is not the proper function of a mental hospital seems to me a verbal quibble. One has has only to read Dr. Houston's imaginative article, A Project for a Mental Health Village Settlement,[2] and Professor McKeown's Balanced Hospital Community[3] to realise the possibilities of the future. I cannot see that mental hospitals can contract out of making such provisions.

Is it sufficient to treat the patient of today as the neighbour of tomorrow? Should we not aim at treating patients as we would like to be treated ourselves?

Shenley Hospital,
near St. Albans,
Hertfordshire. **RUSSELL BARTON**

ULCERATIVE COLITIS

SIR,—We are grateful to Dr. Balfour Sclare (Aug. 9) for suggesting that the questionnaire in our paper of July 19 should have been given in detail. It was omitted to save space, but we would gladly forward a copy to anyone who cares to see it. The patients surveyed do not, of course, represent a "fair cross-section" of all cases suffering from ulcerative colitis: as they were all sufficiently ill to require an ileostomy, milder cases must have been excluded. However, we could say with certainty that every patient did suffer from the disease—which in a more comprehensive series could not be guaranteed. We are pleased that Dr. Sclare agrees with us on our proposed prospective inquiry on a longitudinal basis, but it is of interest that the present questionnaire method has already yielded information which is very close to that of the more detailed long-term studies of Engel. One of us (M. S.) had the opportunity of visiting Professor Engel in his clinic at Rochester, N.Y., after our paper was submitted, and a reconciliation of our statistics revealed many points of similarity: differences originally apparent were due to the methods of presentation.

We can understand the reactions of Dr. Ranyard West (Aug. 9) and Dr. Paulley (Aug. 23) to our inquiry. Most psychotherapists working with patients with ulcerative colitis are quite convinced of the psychological processes "that are causally connected with the symptoms in sufferers from this disease", yet the theories of these psychological processes are many and some are mutually exclusive. We shall not burden your readers with more references, but suggest again that they consult the papers of Engel which we have quoted. A psychosomatic hypothesis should fit in with the essential organic features of the disease and its natural history, and our *preliminary* inquiry into the order of appearance of symptoms in a very large (if not the largest) group of patients with proven ulcerative colitis does not encourage us to accept the existing hypotheses, but to study them even more critically.

We agree that psychotherapy in some patients is of value, but that does not support or prove the seven or eight psychosomatic hypotheses on the ætiology of the disease or tell us which is the most valid. Our paper (a joint effort by psychiatrist and surgeon) was not designed to prove that the condition was not due to psychological happenings. We are not prepared to accept the conviction of others—sometimes based on as few as two or three patients—unless they can be supported by proper evidence. We do not claim infallibility for our preliminary inquiry, but in reply to Dr Paulley's arguments against it we can only repeat "the value of the present method cannot be adequately tested by argument, but only by a carefully controlled prospective inquiry, which we propose to do".

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[1] Martin, D. V. *Lancet*, 1955, ii, 1188.

[2] Houston, F. *ibid*. p. 1133.

[3] McKeown, T. *ibid*. 1958, i, 701.

The Queen Elizabeth Hospital,
Birmingham, 15

M. SIM
B. N. BROOKE.

UNIDENTIFIED DRUGS

SIR,—Patients often come to hospital with tablets which their general practitioners have been giving them for a long time, and the name of which they do not know. The houseman has to find out the name of the drug, and this often results in delay in treatment.

Would it not be better if the general practitioner told the hospital of any chronic illness in a patient referred for some acute condition, and the treatment that is being given? This would be a great help for the inexperienced junior members of the hospital staff, like myself.

St. Albans City Hospital,
St. Albans, Hertfordshire.

BISWARUP BHATTACHARYA.

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—Your annotation,[1] combined with Mr. Charnley's comments (July 5), has reminded me that we lack a basic philosophy which might illuminate our search for the cause of pain. The pathology of pain is ill-understood but accepted in general as pressure; therefore he who first propounds a plausible theory of pressure wins the honours.

But let us examine Mr. Charnley's invention of a suddenly expanded disc causing pressure like that in an abscess.

This is the ghost of turgor again,* and I thought that that had been laid fourteen years ago. Self-expansibility, said Ffrangcon Roberts,[2] is a quality unknown in physics: "to ascribe turgor or power of expansion to the nucleus is to invoke some property quite unknown in the physical world and takes Medicine back to the obscurantism of the Middle Ages".

Instead of turgor, Mr. Charnley calls it hydrophilia: dried discs swell when placed in water. Of course they do, as does any piece of dead cartilage. The disc is nothing but a resilient bit of fibrocartilage, more cartilaginous at its centre and more fibrous at its margin. Nucleus pulposus and annulus fibrosus are verbal expressions and not entities. Like other cartilaginous structures the disc cushions sudden or intermittent pressure by flattening, and it is restored to its previous shape when the compressing force is removed. Its resilience is shown by the rarity of disc lesions in compression fractures of the vertebral bodies.

Like other cartilage, the disc cannot have a weight-bearing function; continuous pressure causes its absorption or degeneration. The weight-bearing structures in the back are the pedicles and articular processes; narrowing of an intervertebral disc is always secondary to failure of these structures through decalcification.[3] Narrowing of the space, therefore, is not the cause of the pain but a later effect of the decalcifying process.

I am glad to read (1) that Mr. Charnley has never seen the actually swollen discs; (2) that protrusions are rare in acute lumbago; (3) that pain in acute lumbago is not proportional to the change in the disc. Could this not possibly mean that the disc is not the cause of the pain—that the pain, as elsewhere, arises in muscular, synovial, or ligamentous structures?

MICHAEL KELLY.

* [illegible]

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[1] Lancet, 1958, ii, 4.

[2] Roberts, F. [illegible]

[3] Roberts, F. [illegible]

LEARNING TO LEARN

SIR,—The Students' Guide (Aug. 30) outlines present-day medical education in your usual lively manner. Especially interesting is your treatment of the faculty of learning. Teachers, absorbed in planning curricula, overlook that even more important than the science of teaching is this art of learning. Not all of us have to instruct, but we all need to assimilate, and we painfully rediscover what Hippocrates told us—that in a brief lifetime it takes a long while to learn. We get less from regular teachers than from irregular sources. How can we best acquire a habit of receptivity to unconventional means of knowledge? Of course, each of us must work out his private technique.

Learning does not deal with external knowledge alone; we have to revalue our own capacity for handling experience. In the past, many doctors changed over to a line of medicine different from that in which they began. What this means is that they fashioned their own curriculum later than the average. General practitioners sometimes became successful consultants, for the best of all reasons—they found that people wished to consult them. A young doctor today is not encouraged to change his course, but for any individual the start of true learning may be the moment he realises he had taken a wrong direction. Some advice from late beginners, who found a vocation through their own efforts and not from teachers, would be illuminating next year.

London, W.C.1.

HARLEY WILLIAMS.

GLUTETHIMIDE POISONING

SIR,—A patient with glutethimide poisoning has previously been reported from this hospital by one of us.[1] It was noted at that time that respiratory depression was very slight, that the condition responded to the administration of bemegride and amphenazole, and that the patient, during the period of coma, had attacks of laryngeal spasm closely resembling tetany. These attacks were exacerbated by the administration of bemegride. We have recently seen the identical features in another patient with glutethimide poisoning.

A married woman, aged 39, who had a long history of depression, was admitted to the Royal Victoria Infirmary on July 31, 1958, in deep coma. Three and a half hours before admission she had taken 22 tablets (5.5 g.) of glutethimide ('Doriden'). Her pupils were of normal size and failed to react to light, and the corneal reflexes were absent. The tendon jerks were depressed and the plantar responses were flexor. Respiration was not markedly depressed. Gastric lavage was performed and bemegride administered as a continuous intravenous infusion: in all, 850 mg. was given in two hours. The limb reflexes returned within thirty-five minutes and the corneal reflexes within three hours of starting bemegride.

Soon after admission intermittent attacks of spasm of the limbs, associated with tetanic spasm of the hands, were noted. Trousseau's and Chvostek's signs were negative, the serum calcium and phosphorus were normal, and intravenous calcium gluconate was without effect. Bemegride increased the spasms. The patient also had intermittent head retraction and attacks of laryngeal spasm. The muscles in spasm changed frequently, both flexor and extensor groups being involved intermittently and more independently in all four limbs. This resulted in an appearance in the upper limbs sometimes suggesting tetany and sometimes a posture reminiscent of [illegible]. The attacks of spasm decreased in severity and disappeared within fourteen hours.

The clinical features of this case were so similar to those of the previous one that we feel that there is an [illegible] that the attacks of muscle spasm were due to glutethimide. The site of action remains obscure, but, in view of the changing posture of the limbs, this may be in the corpus striatum

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[1] [illegible] N. R. Lancet, [illegible]

This case underlines the safety of the therapeutic dose of glutethimide, and also that it is a suitable sedative for patients where respiratory depression should be avoided Bemegride is indicated in cases of poisoning

Royal Victoria Infirmary,
Newcastle upon Tyne, 1

A R HORLER
N R. ROWELL

MIDGET ANÆSTHETIC MACHINES

SIR,—With reference to Dr Burton's letter last week, the universal adoption of the B S I pin index fitting for medical gas cylinders should facilitate the development of lightweight anæsthetic machines

We have had in use for six months an apparatus weighing 7 lb that can be fitted with any size of pin index cylinders The basis of the apparatus is combined cylinder yokes, regulators, and plastic flowmeters for the gases The fittings are standard anæsthetic equipment so that additions or replacements are easily available. A full range of gases can be used and any standard vaporising bottle included in the circuit. The similar heads for all sizes of the new cylinders together with the use of lightweight alloys in the machine allow the machine to serve in daily use and as a portable emergency apparatus

Royal Marsden Hospital,
London, S W 3

J D K BURTON

THE PLACE OF THE RESEARCH INSTITUTE IN THE ADVANCE OF MEDICINE

SIR,—Sir Charles Harington's article[1] will have been read with great interest by medical research workers everywhere. As his closing theme he mentions the difficulty of establishing sufficient contact between the laboratory research institute and the sick patient, and considers the possible advantages of establishing institutes for clinical research.

Conditions in Malaya are very different from those in England, but this Institute for Medical Research has over a few decades achieved a fortunate blend of laboratory and clinical work.

The Institute itself has no beds, but is situated next to a large general hospital When a patient is admitted to the hospital with an illness known to be of interest to one of the Institute staff, we are notified, and, if after initial examinations the patient is deemed suitable for further research studies, the hospital physicians have generously allowed us to take over complete control of the patient while retaining the use of the hospital bed. This has been practised in the study of such diseases as beriberi, malaria, filariasis, and the nutritional anæmias

This happy state depends entirely upon the good will and confidence between the hospital and Institute staff at the personal level—a trust which has been built up for half a century

Such a system has the great advantage of flexibility, for when the study of any particular problem has been completed it is easy to pass to another by drawing upon a different type of patient in the large hospital pool

Many of the difficulties in tropical medical research are avoided by this efficient system, which allows maximum information to be gained from the material at hand. Experience here bears out Sir Charles Harington's view that such a combination of clinical and laboratory research can provide valuable results

Institute for Medical Research,
Kuala Lumpur, Malaya.

P W G TASKER

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1 *Lancet*, 1958, i, 1345

FERTILITY AND MENTAL ILLNESS

SIR,—In your leading article of Aug 16 you refer to a finding that "schizophrenics were as a whole about a quarter as fertile as the general population" It may be of interest to point out that Reiss and Hemphill[1] have shown that in many advanced schizophrenics there is vascular degeneration of the testes, this could undoubtedly have had an effect on the lowered fertility I have also noted the relation between hypothalamic disturbances and impaired fertility, and many men suffering from such conditions are infertile In two cases of narcolepsy there was severe infertility, and other observers have already noted this connection It may well be, therefore, that there is an organic basis to be taken into account as well as the "premorbid schizoid personality" making marriage less likely to which you refer

Manchester

BERNARD SANDLER

CARDIAC COMPLICATIONS OF COXSACKIE-VIRUS INFECTION

SIR,—We have already described[2] infection with Coxsackie virus type B4 as a cause of benign pericarditis Recently another of these cases has shown evidence of infection with Coxsackie virus type B3, and we would like to draw attention to the signs of cardiac involvement.

A man, aged 50, contracted an acute febrile illness which lasted for 5 days The onset was sudden with shivering, sharp pains in the chest, and considerable dyspnœa The initial temperature was 102 4°F There were crepitations over the lower lobe of the right lung, and pericardial friction was audible over the precordium, especially at the base of the heart. The heart rhythm was regular, rate 100 per min. X-ray of the chest on the day of admission showed moderate cardiac enlargement and an area of "ground-glass" consolidation in the lower lobe of the right lung An electrocardiograph at this time was abnormal, the T waves were negative in leads I, aVL, and V_{1-6}, with slight elevation of the S-T segments In association with the clinical findings these changes may be regarded as evidence of cardiac involvement with pericarditis Ten days later the electrocardiograph had reverted to normal, and repeat X-ray of the chest showed that the heart was now normal in size, and the consolidation of the right lung had resolved. Also the patient had made a complete clinical recovery

Results of neutralisation tests for Coxsackie virus type B in tissue culture (monkey kidney) carried out by the Virus Reference Laboratory, Colindale, London, were

Specimen	*Day of illness*	*B1*	*B2*	*B3*	*B4*	*B5*
1	9			1/80		
2	23	<1/10	<1/10	<1/80	<1/10	<1/10

Subsequent neutralisation tests over a period of three months showed titres of 1/64 for type B3 Routine laboratory investigations revealed no other significant features to account for the febrile illness white blood-cells 9450 per c.mm , anti-streptolysin titre positive 1/20 and negative 1/40, throat swab, *Streptococcus viridans* The patient's convalescence was uneventful, and recovery was complete

The neutralisation tests support the view that the patient had a Coxsackie-virus infection type B3 The acute febrile illness is typical of such an infection, especially the chest pains and pulmonary complications Cardiac involvement in Coxsackie-virus infection is becoming more widely recognised, and this case of type-B3 infection adds to the ætiological factors of benign pericarditis

Belfast City Hospital

EVAN FLETCHER
C F. BRENNAN

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1 Reiss M., Hemphill, R. E. *J ment Sci* 1944 90, 681
2. Fletcher, E., Brennan, C. F *Lancet*, 1957, i, 913

HOW TO BE HAPPY THOUGH RESIDENT

SIR,—Hospital administrators will read with lively appreciation the homily addressed to residents by Mr Jennett, especially the reference to their relations with other departments of the hospital

At this hospital, and doubtless in many others, an invitation is extended to the residents, upon taking up their posts, to meet the chief administrative officer in an endeavour to start off on the right foot, when assurance is given of the fullest cooperation by the administrative staff

Although this is probably only practicable in medium-sized hospitals, experience shows that the simple gesture is usually appreciated

Wembley Hospital P E WINDO

DISSEMINATION OF MICROORGANISMS BY A SURGICAL PUMP

SIR,—The article by Mr Ranger and Dr O'Grady (Aug 9) revealed a possible, even likely, source of cross-infection in wards where mechanical suction is commonly used Their remarks relate to the Middlesex type of machine, and they recommend an effective remedy

This prompted a survey of all suction pumps in this group of hospitals, and the results of a few simple experiments show that we, at any rate, have been somewhat complacent

The group possesses two diathermy machines with suction pumps, five of Guy's Hospital type, three of Middlesex type, and two of uncertain breed The Middlesex machines are being dealt with as suggested by Mr. Ranger and Dr O'Grady and are now safe But the diathermy machines have no filter, and the exhaust is under the casing and discharges directly on to the floor The Guy's type are fitted with filters consisting of two felt discs which are secured to the back of the machine by a metal case of which the outer half is secured by two small, grub-like screws which are awkward to remove and worse to replace

The accompanying table shows the results of the admittedly primitive experiments

It is evident that there is a potential danger from suction pumps, even when provided with a filter, if the filtering material is not replaced after use in a septic case Ranger and O'Grady found that higher negative pressures produced more organisms at the outlet, but they refer to vacuums of 5–20 cm Hg The Guy's machine and the diathermy machines are designed to give up to 30 inches Hg! Possibly this is why surgeons seem to prefer them

RESULTS OF BACTERIAL CULTURES

Source	Type of machine	Culture
Theatre I	*Guy's* Inner disc Outer disc	*Staph albus*, *B subtilis*, *Bact aerogenes*, *Ps pyocyanea* *Staph albus*, non-hæmolytic streptococci, *Bact aerogenes*, *B subtilis*
Theatre II	*Guy's* Inner disc Outer disc	*B subtilis*, paracolon bacillus, hæmolytic anaerobic streptococci (group G) *B subtilis* paracolon bacillus
Theatre III	*Guy's* Inner disc Outer disc	*Bact alkaligenes*, *B subtilis* *B subtilis* only
Children's ward	*Guy's* Both discs	Coagulase-negative *Staph aureus* and an unidentified micrococcus
Neonatal ward	*Guy's* Inner disc Outer disc	*B subtilis* Sterile
Theatre I*	*Diathermy*	*Ps pyocyanea*
Theatre II*	*Diathermy*	*Staph albus* overgrown by *B subtilis*

* Obtained by holding a sterile celloidin membrane to the exhaust for three or four seconds

Splashing always occurs in the container when the cavity being drained empties, or when the machine is switched off, and some organisms are bound to be drawn into the pump, and are ejected when it is next switched on Contamination of the pump is naturally greater when suction is applied intermittently

The remedy, in the case of the Guy's type of machine, is to replace the small screws by a spring clip, which permits changing of the filter discs without tears The diathermy machines call for ingenuity in devising a trap which will not reduce the efficiency of the vacuum, probably enlarging the outlet hole, and leading a copper pipe to a trap attached to the machine, will meet most cases

Victoria Hospital,
Worksop, Notts GAVIN DUNLOP

FALSE GLYCOSURIA

SIR,—Bottles containing specimens of urine are brought to the general practitioner for testing When one uses the newer preparations for rapid testing for glucose, mistakes may arise when the bottle contains contaminants

Two specimens of urine brought to me in this way on successive days showed considerable glycosuria when tested by 'Testape' and 'Clinistix', but both specimens failed to reduce Benedict's solution

Both bottles had contained hydrogen peroxide, and, even though they had been washed before use, there was sufficient solution soaked in the screw cap to give a misleading result

Although this must be an uncommon incident, the fact that hydrogen peroxide may mimic glycosuria in the rapid test should be borne in mind to save an occasional patient from unnecessary concern

London, E 9 ALEC PHILLIPS

DIAGNOSIS OF SICKLE-CELL ANÆMIA AFTER BLOOD-TRANSFUSION

SIR,—Severe anæmia is commonly seen in the children's department at University College Hospital, Ibadan It is usually caused by malaria, malnutrition, or hookworm infestation or a combination of these, but it is quite often sickle-cell anæmia From time to time a severely anæmic child is admitted and transfused before appropriate investigations have been undertaken to establish the diagnosis of sickle-cell anæmia (The presence of the transfused normal erythrocytes in the patient's circulation interferes with interpretation of the hæmoglobin electrophoresis) Under these circumstances it has been our practice to defer hæmoglobin electrophoresis, to establish the diagnosis of sickle-cell anæmia, until the transfused cells have disappeared from the circulation—usually a period of 3 to 4 months The technique described below has recently been evolved in our departmental laboratory to obviate the time-lag in establishing the diagnosis

The erythrocytes of normal individuals are usually completely lysed in 0 3% sodium chloride solution,[1] whereas in sickle-cell anæmia lysis usually only commences in 0 34% sodium chloride and is often complete only in 0 01% sodium chloride[2] It is to be anticipated thus that lysis in 0 3% saline of blood obtained from a patient with sickle-cell anæmia after transfusion will result in destruction of all the normal cells,

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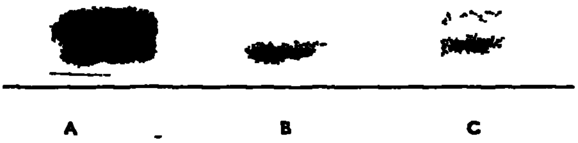
1 Dacie, J V The Hæmolytic Anæmias London 1954
2 Diggs, L W, Bibb, J *J Amer med Ass* 1939, 112, 695

leaving intact only cells containing sickle hæmoglobin. A hæmoglobin solution prepared from the remaining cells would be expected to show only the abnormal hæmoglobin The



accompanying illustration shows the result of filter paper electrophoresis of different hæmoglobin solutions prepared from the blood of a patient with sickle-cell anæmia immediately after transfusion. Solution A was prepared by lysing all erythrocytes in distilled water Solution B was prepared from cells which resisted lysis in 0 3% saline Solution C is an A/S control It will be seen that while A shows an A/S pattern, B shows hæmoglobin S only

In sickle-cell/hæmoglobin-C disease and homozygous hæmoglobin-C disease the erythrocytes also show increased resistance to hypotonic saline solutions, and it is probable that these conditions could also be diagnosed with certainty in a recently transfused patient by employing this technique

University College,
Ibadan, Nigeria

R G HENDRICKSE

YOUTH CLUBS FOR THE HANDICAPPED

SIR,—Before retiring from the presidency of the Handicapped Children's Club, Bexleyheath, Kent, I should be grateful for the use of your columns to bring to notice the existence of this and similar organisations throughout the country

The Bexleyheath club started in March, 1954, under the auspices of the local Society for Mentally Handicapped Children and was reorganised in September, 1955, as an independent Handicapped Children's Club in order to cater for children with any type of mental or physical handicap At present there are 23 members (13 males and 10 females) and the majority are mentally defective (The remainder include spastics, educationally subnormal, and maladjusted children.) The age range is 10 to 33 years with mental ages of approximately 3 to 9 years Accommodation is provided in a local modern school and includes the use of a large hall, classrooms, garden, and playing-fields Play materials are obtained by purchase from club funds and gifts from supporters, in addition, the school authorities have kindly granted the use of equipment The regular staff consists of experienced and sympathetic voluntary workers, including 5 teachers from junior schools, 3 from occupation centres, and a few nursing and teaching students (the ratio of staff to members is roughly 1 to 3) Meetings take place fortnightly during the school term and are always well attended.

In April, 1956, an Independent Committee for Youth Clubs for the Handicapped was formed to promote the development of similar clubs in other areas A cine colour film, taken of the children's activities during the previous year, was shown in several districts of Kent and within 5 months a chain of clubs extended across North Kent The success of this venture encouraged the committee to show the film in London and the South-Eastern Counties, and by January, 1958, 17 new clubs had opened My latest information is that the campaign has spread to four other counties, 9 new clubs have been opened, and 17 districts are organising facilities

I feel these clubs fulfil a useful function in the socialisation and education of handicapped children, and they afford the parents an opportunity to enjoy regular and frequent contact, thereby reducing their sense of isolation The staff members, visiting speakers, and club library also help to dispel many misconceptions and old wives' tales concerning mentally handicapped children and thus alleviate much of the parents' self-blame and guilt In addition, the club serves a more general function in the promotion of mental health by acting as a focal point of local interest in mental handicap, where individuals and organisations interested in this work may congregate, and where visitors from all sections of the public are welcome

Further particulars regarding youth clubs for the handicapped may be obtained from Mr J B Millwood, hon secretary, 18, Martin Rise, Bexleyheath, Kent (telephone Bexleyheath 7331)

Clatterbridge Hospital,
Bebington,
Cheshire.

D M ZAUSMER

THE TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

SIR,—Dr Watson-Williams and his colleagues (Aug 2) mention that they failed to find a recorded instance of a steroid-induced remission in a patient with a long history of purpura A case I reported of an Indian boy who developed purpura in 1949 and had a temporary remission after splenectomy[1] may therefore be of more interest than I suspected

In 1954 he was started on corticosteroid therapy and he has since been well controlled successively on cortisone, prednisone, prednisolone, and triamcinolone He has now had a continuous remission of twenty-three months to date this is certainly steroid-induced, for repeated attempts at reduction in his maintenance dosage of corticosteroids have resulted in prompt thrombocytopenia and bleeding gums Of the corticosteroids used in this case, triamcinolone has had the greatest therapeutic potency and has also been the most effective

General Hospital,
Singapore

RONALD WELLS

STORAGE OF INULIN IN RENAL TISSUE

SIR,—According to most authors inulin is the ideal substance for the determination of the glomerular filtration-rate There is, however, in oliguric states a discrepancy between the clearances determined by the classical method and by the constant-infusion technique without collection of urine Part of the infused inulin must thus be metabolised and/or excreted extrarenally and/or deposited in the organism We have been interested in the storage of inulin in renal tissue

Having re-examined the fact that, in spite of a constant plasma-inulin level, the excreted quantity is well below the infused one, we found that there is about 1 17–4 03 mg of inulin per g of kidney substance This quantity, although significant, is too small to explain the difference between the infused and excreted amount during a clearance experiment of average duration

In another experiment dogs made oliguric by hæmorrhage were given an infusion of inulin The left kidney was then transplanted to the neck of a second dog, which was not given inulin The urine of the transplanted kidney, as well as the recipient's urine, was collected until free of inulin, and the whole excreted quantity of inulin determined The transplanted kidney was then analysed for the remaining inulin The sum of the three quantities was in fair agreement with the inulin content of the right kidney removed at the same time as the transplantation of the left kidney

The right kidney contained 1 03–5 75 mg inulin per g, the transplanted left one, having been "washed out" by the inulin-free blood and its own urine, contained only 0 22–1 84 mg per g (In 1 case we found 5 10 mg per g)

Our experiments seem to prove that some of the inulin infused can be stored in the kidney Part of this quantity seems to be in the dead space of the urinary tract, part of it in the renal vessels and interstitium There is, however, a small but significant quantity of inulin which remains stored in the renal tissue proper

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[1] Wells, R *Proc Alumni Ass Malaya*, 1957, 10, 226

Nevertheless, this seems to be too small to explain the diminished clearance values in oliguria, and an extrarenal disposition of inulin has to be supposed

A detailed account of our data is to be published in *Acta physiologica hungarica*

Physiological Institute,
Medical University,
Budapest

P BÁLINT
I FORGÁCS

"INCIDENCE" OF HYALINE MEMBRANE IN PREMATURE INFANTS

SIR,—We should like to call attention to a certain amount of confusion which exists with respect to estimates of the incidence of hyaline-membrane disease among premature infants Since there is no infallible method of establishing this diagnosis during life, it has been the usual practice to determine the presence of this condition from the microscopic appearance of the lungs at necropsy The incidence has then been computed as follows (hyaline membrane/total necropsied infants) × 100 = % incidence On the basis of these calculations those interested in this problem have been hard pressed to explain the high incidence of this condition among premature infants in the middle birthweight groups and the lower incidence among the lightest newborns

We have examined our experience over a 7-year period (1950–57) in the premature nursery of the Babies' Hospital During this interval 692 infants whose birthweight was less than 2001 g were admitted to the premature nursery following birth in the Sloane Hospital for Women, the intramural obstetrical service of the Columbia-Presbyterian Medical Center During the first three days of life 197 of these infants died Necropsies were performed on 150, and 86 were found to have hyaline membrane in the lungs

The "incidence" of this condition among these prematures is, of course, influenced markedly by the choice of a denominator population Since we were interested in determining the *influence of the degree of prematurity* upon the incidence of this condition, and since the mean age at death is later for large than for small premature infants, we calculated rates specific for birthweight and age at death, and they appear in the accompanying table

As can be seen the proportion of individuals examined at necropsy among those who died in the various age and birthweight categories was essentially the same Therefore, we have reckoned the "incidence" to be the number of examples of hyaline membrane at necropsy among the total number of infants admitted (less those who died in the previous age interval) For the purpose of this calculation we have made the assumption that the mortality-rate associated with hyaline-membrane disease was the same in the three birthweight categories

These estimates of the incidence of hyaline-membrane disease indicate that the condition occurs with equal or greater frequency among the lightest premature infants If these approximations prove to be related to the true incidence of hyaline-membrane disease, we may have nothing to explain except the factor of prematurity itself

"INCIDENCE" OF HYALINE MEMBRANE

Birthweight		≤ 1000 grammes	1001–1500 grammes	1501–2000 grammes
	No of infants admitted	116 infants	216 infants	360 infants
Died 0–23 hours	Died	56	33	20
	Necropsies	52	32	18
	Hyaline membrane	15	24	14
	% necropsied cases affected	(15/52) 29%	(24/32) 75%	(14/18) 78%
	'Incidence' in total population	(15/116) 13%	(24/216) 11%	(14/360) 4%
Died 24–47 hours	Died	22	21	21
	Necropsies	20	17	19
	Hyaline membrane	3	9	14
	% necropsied cases affected	(3/20) 15%	(9/17) 53%	(14/19) 74%
	"Incidence" in total population	(3/116–56) 5%	(9/216–33) 5%	(14/360–20) 4%
Died 48–71 hours	Died	9	8	7
	Necropsies	8	8	6
	Hyaline membrane	1	2	4
	% necropsied cases affected	(1/8) 13%	(2/8) 25%	(4/6) 67%
	"Incidence' in total population	(1/116–56–22) 3%	(2/216–33–21) 1%	(4/360–20–21) 1%

We suggest, speculatively, that other conditions associated with an increased incidence of hyaline-membrane disease (e g, maternal diabetes, cæsarean section, and placenta previa) may prove to be related only as the result of a common and unhappy association with prematurity

WILLIAM A SILVERMAN
Babies' Hospital, New York RUTH H SILVERMAN

GLOVES FOR NURSES

SIR,—The ineffectiveness of ordinary hand-washing is shown by the results of investigations on the bacteriology of the finger-tips of nurses

In these investigations, which have been carried out regularly here for nearly three years, each nurse, straight from duty in the wards, presses the tips of the unwashed index, middle, and ring fingers of the right hand on the surface of half a sterile blood-agar plate The nurse then washes her hands with toilet soap and hot water under a running tap, and dries *both her* hands on her individual sterile towel The washed and dried index, middle, and ring fingers of her right hand are then again pressed on the surface of the second half of the sterile blood-agar plate The blood-agar plate is incubated at 37°C for forty-eight hours and the colonies "before" and "after" are counted (1) after twenty-four hours' incubation, (2) after forty-eight hours' incubation, and the counts are recorded The plates are then kept covered for some weeks on the bench at room-temperature and examined from time to time for late developers Almost equal numbers of colonies develop in the "before" and "after" halves of the blood-agar plate

In another series of experiments, the procedure was the same except that "after" the nurse dipped her dried fingers into strong commercial methylated spirit up to the proximal phalanx for exactly sixty seconds The plate-counts "before" were unaltered, but the "after" counts were significantly altered—in fact, the "after" half of the plate was usually sterile More than a hundred experiments on these lines were carried out, with results that varied only slightly

We concluded that nurses should wear thin sterile rubber gloves when performing the following tasks washing and shaving a patient before operation; washing a patient after death and preparing the body, routine washing of a patient, passing a catheter and obtaining a sterile specimen of urine, changing the napkins of a baby and cleaning its bottom, changing wound dressings, giving a patient a bedpan or urinal, cleaning the patient and taking the bedpan or urinal to the sluice, and handling these objects while washing and sterilising them, if these operations are done by hand, changing stained bed linen, counting dirty linen (better to count the linen after laundering); giving streptomycin injections and filling the syringe, handling sputum pots, sputum jars, fæcal-specimen jars or pots, and swab-tubes, giving enemas, taking rectal swabs, manipulating colostomy tubes, and handling empyema and other drainage tubes Gloves also protect the skin of the nurse's hands from too frequent washing and drying

In the interval between any two tasks, and while performing a lengthy task, the nurse dips her gloved hands into a dilute disinfectant such as dilute watery chlorinated lime, chlorhexidine, or even tricresol, and dries her gloved hands on a sterile towel

In the absence of gloves, the conscientious nurse, following popular teaching, may find it necessary to wash and dry her hands more than a dozen times in a working day This repeated washing and drying is bound to injure the epidermis and cause the hands to become rough and dry and cracked This deterioration of the state of the skin is very serious, proper asepsis cannot be attained, and the nurse may develop a whitlow, which may incapacitate her for a week or more When her lesion has healed, and she returns to work, the repeated washing and drying of her hands will start her troubles all over again We are driven to the logical conclusion that the nurse should wear thin sterile rubber gloves, to prevent cross-infection and to protect her hands while at work

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FRANK MARSH

RESERPINE IN SCHIZOPHRENIA

SIR,—Although reserpine ('Serpasil') has now been used widely in the treatment of schizophrenia it might be of interest briefly to record the results of this treatment in a small mixed group of patients during the period May, 1956, to May, 1957

The 35 cases in this group consisted of insulin failures and relapses, or cases considered unsuitable for insulin therapy, thus, those with the best prognosis were excluded. Except that the patients were, in most cases, recent admissions, no other factors entered into their selection

At the start of treatment, dosage varied from 8 5 mg to 11 5 mg daily for about six weeks It was then gradually reduced, during the subsequent six to eight weeks, to 0 75 mg daily The duration of treatment varied from three or four months to a year, according to the duration of symptoms before treatment began and the willingness of the patient to cooperate after discharge from hospital To minimise the risk of a suicidal depression, relatives were advised in writing to inform their doctor if the patient should become depressed and the doctor was advised to inform us Most patients were discharged on trial for three to six months to give us further control of therapy Definite depression, a rare occurrence, indicated cessation of treatment.

After discharge from hospital, patients received routine visits from the psychiatric social worker and were followed up at the outpatient clinic at two to four weekly intervals While in hospital they had weekly interviews Supervision continued for an average of six months to a year

Patients were classified as "recovered" if they were fully socialised and revealed no overt psychotic manifestations, and as "relieved" if definite improvement rendered them capable of partial socialisation with marked diminution of psychotic symptoms The results were as follows

I Simple—2 cases of long duration Failed

II Hebephrenic—9 cases 4 recovered (2 cases were of over two years' duration and 2 of short duration) 3 relieved, 1 since relapsed (all over two years' duration) 2 failed (1 over two years and 1 probably over two) 6 (67%) recovered and relieved in all (omitting relapse)

III Paranoid.—19 cases 9 recovered (4 over two years, 5 of short duration) 3 relieved (1 relapsed since, all over two years) 7 failed (all over two years) 11 (58%) recovered and relieved in all (omitting relapse)

IV Catatonic.—3 cases 1 recovered (short duration) 2 failed (over two years)

V Puerperal—2 of brief duration 1 recovered, 1 relieved

In I, IV, and V the numbers were too small to be significant. From such a small group no definite conclusions could be drawn, but we would record our clinical impressions

(1) The cases most suitable for this form of therapy seem to be the colourless, apathetic type of hebephrenic We also noted that the paranoid patients most helped revealed a flattened affect, lack of colour, and spontaneity Patients with more colourful effect appeared to respond more satisfactorily to chlorpromazine.

(2) We feel it is important to continue serpasil in small doses, in cases of long duration, for upwards of a year, perhaps longer This appears to lessen the likelihood of relapse We had no case relapse while on maintenance treatment.

These comments are based on our hospital records up to June 30, 1958

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PRODUCTION OF LUNG CONSOLIDATION IN MICE BY STAPHYLOCOCCAL TOXINS

SIR,—Mice of mean body-weight 12 g, inoculated intranasally with a dose of from 0 1 to 1 2 mg of *Staphylococcus aureus* (Terajima strain) under light anæsthesia did not die, and only a slight congestion of the lungs, without abscess formation, was observed The inoculated organisms were gradually eliminated from the lungs within a few days But each mouse inoculated intranasally with 0 05 ml of a potent filtrate of the culture (prepared by the method described below) died with extensive hæmorrhagic consolidation of the lungs There was intensive congestion, œdema, and hæmorrhage but no abscess formation The filtrate plus the staphylococci produced extensive consolidation *with* abscess formation

Staphylococci were cultured in a semisolid agar (pH 7 2) consisting of 2% peptone, 0 2% agar, 0·3% NaCl, 0 2% potassium phosphate, and 0 03% magnesium sulphate, in an atmosphere of 20% CO_2 at 37°C for 48 hours The culture was centrifuged and the supernatant was filtered with Seitz EK to remove the organisms The activity of the cell-free filtrate was titrated and the titre expressed as the highest dilution causing complete hæmolysis of rabbit erythrocytes in a 0 5% suspension after 1 hour's incubation at 37°C Although the titre of the filtrate and the time till death of the inoculated mice was in an inverse relation, the limiting titre for cause of death was about 100

The following experiments were made with a filtrate with a titre of 1600 as a consolidation-producing dose which brought about death within 14 hours The power of producing consolidation and the hæmolytic activity of a filtrate were lost by heating at 60°C for 30 min., by treatment with formol (0 4‰, 1 week incubation), or by treatment with a sufficient amount of rabbit red cells at 0°C (indicating the adsorption of the active substances to the red cells) An antiserum prepared by immunising a rabbit with formolised filtrate neutralised the consolidation-producing toxicity in vitro These results suggest the presence of an intimate relation between alpha-hæmolysin[1] and consolidation-producing factor in the filtrate.

Each mouse was injected subcutaneously with a dose ranging from 100 to 500 µg. of tetraethylammonium bromide (T.E.A.), and 30 min later a consolidation-producing dose of a filtrate was given intranasally None of the mice died within 72 hours, and when killed they showed no consolidation. Each mouse of another group was injected subcutaneously with a dose ranging from 50 to 500 µg of chlorpromazine, and 30 min. later a consolidation-producing dose was given intranasally As in the case of T E A none of the mice died within 72 hours, and none showed pulmonary consolidation

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[1] Glenny, A. T, Stevens, M F *J Path Bact* 1935, 40, 201

Penner and Klein [2] observed that direct contact of shiga neurotoxin and intestinal mucosa of dogs produced no lesion in the intestinal mucosa, whereas an intravenous injection of the toxin caused the appearance of a number of focal lesions, and that this phenomenon could be inhibited by injection of tetraethylammonium chloride

We [3-5] have reported that each particle of influenza virus (PR8), Newcastle disease virus, or hæmagglutinating virus of Japan can cause, even when infectivity has been destroyed, pulmonary consolidation in the inoculated mice, and that the production of consolidation is completely prevented by a previous injection of an adequate dose of T E A or chlorpromazine Since these drugs interfere with the passage of autonomic impulses through the central nervous system, it appears that staphylococcal toxins, like shiga neurotoxin or some viruses, have their primary action on the nervous system itself

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KAZUO OGASAWARA
SHOSHI TANAKA

SINGLE DAILY DOSE OF CHLORPROMAZINE

SIR,—In my letter [6] last March, I described a trial of treatment of patients on a single *daily* maintenance dose of chlorpromazine, and mentioned that other wards than the "pilot" ward had since followed up this idea with success

Further experience in these other wards shows that this success is only partial although the original pilot ward has carried on satisfactorily Of a total of 70 female patients on chlorpromazine in two large chronic refractory wards, where this method has been tried, it has proved possible to maintain satisfactory results in 32 patients only (45%) There were no real problems during the first weeks after the change to daily dose, but gradually it became necessary to change and divide the dosage because some patients were unduly drowsy during the day, because some patients appeared pallid and listless or complained of vague malaise, and because, as is often the case on these wards, individual patients' pattern of illness required changes in medication.

I thought it necessary to make this further report, in that this experience serves strongly to reaffirm the necessity of constantly regulating dosage to the individual needs of patients

All Saints Hospital, Birmingham

J C N TIBBITS

TEXTBOOKS A NEW STYLE?

SIR,—The publication of a textbook in a cheap utility edition deserves your welcome (Aug 30, p 451), but it is no more than a hesitant step in the right direction The cheap edition referred to costs about 60% of the standard edition—itself an abbreviated 220 pages The suggestion that cheap textbooks could be obtained by limiting their contents does not solve the major problem The need is not for more short textbooks, but for cheap paper-back editions of the large standard textbooks

Few students can afford all the necessary textbooks at four or five guineas each We are further deterred from buying by the rapidity with which new editions appear, causing medical value, and financial value on the second-hand market, to depreciate alarmingly fast

It is clear that some subjects—for example, therapeutics—depending less on illustration are best suited to production on cheap paper But the Pelican books on art and architecture show that both photographs and line drawings can be adequately represented in cheap paper-back volumes Size should be no deterrent, if *War and Peace* can be published in two volumes for ten shillings, let a surgical textbook be published in three volumes for twice as much If the publisher, following Continental custom, produces a really cheap edition with the pages still stuck together, no matter, here at last is a sure way for the student to find out what parts of the syllabus he has not covered

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London, S E 1

S R MEADOW

THE GENERAL PRACTITIONER

SIR,—In his speech in the Lords' debate which you reported on July 12, Lord Moran spoke of a general decline in the status of the general practitioner

It began, he said, "when people generally felt when they were seriously ill that they were well advised to go into hospital That was extremely mortifying to the doctor He found that the patient, in this particular crisis in his life, preferred to put himself into the hands of a complete stranger" [1]

Unfortunately I have not kept statistical records, but on looking through my files I find that, in my five-and-a-half years in general practice, 116 of my patients have been content to die under my care, as against 15 who have died in hospital (3 of whom were admitted as surgical emergencies and 2 had no choice, being certified and carried off willy-nilly) This leaves aside two or three who made no decision either way, and were taken care of by the coroner, but it scarcely bears out Lord Moran's contention, unless one assumes that people who prefer to die in their own beds do not regard themselves as seriously ill

Admittedly many patients do go to hospital, but many return to their own doctor's care The visiting-list of a general practitioner which you published on July 5 should give pause to anyone who supposes that the illnesses of general practice are trivial or that the family doctor finds himself without heavy medical responsibilities

Kingston-on-Thames, Surrey

CHARLES STEER

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

SIR,—Mr Huckstep and Dr Bodkin (Aug 16) give an interesting account of the use of vagotomy to relieve painful hypertrophic pulmonary osteoarthropathy associated with bronchial carcinoma I should like to record a case in which relief was given by a simpler method

A man of 53 had bacteriologically proved pulmonary tuberculosis in 1955, for which segmental resection was performed A hilar glandular mass appeared seven months later, and at thoracotomy an undifferentiated squamous-cell carcinoma was removed

After another nine months he was readmitted with clubbing and fever, and painful œdema of hands and feet which had caused him to be bedridden for two weeks (No finger clubbing had been present after the first operation) As he appeared to have local recurrence of his growth, and hepatomegaly presumably due to metastasis, and as the condition of the extremities and fever were his only symptoms, he was started experimentally on a course of butazolidine, 200 mg twice daily, on May 5, 1957 This was gradually reduced to 100 mg daily The fever and œdema of hands and feet disappeared dramatically, although some clubbing of fingers and toes remained He was discharged home ambulant a month after starting the drug

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[2] Penner, A, Klein, S *J exp Med* 1952, 96, 59
[3] Ogasawara, K, Nakayama, M *Virology* (in the press)
[4] Ogasawara, K, Aida, M *Virus, Kyoto*, 1958, 8, 242
[5] Nakayama, M *ibid* p 262
[6] *Lancet*, 1958, i, 689

[1] Parliamentary Debates (Hansard), House of Lords, July 2, 1958, col 469

Unfortunately he died at the end of 1957, but the painful œdema of the hands and feet did not recur while he was receiving butazolidine, which was continued for about four months in all

In cases of this kind it may be worth trying butazolidine before embarking on vagotomy

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DIANA OWEN

HÆMOPHILIA-LIKE STATES IN GIRLS

SIR,—I read with great interest the article by Professor Quick and Miss Hussey in your issue of June 21, and I want to emphasise the following findings We, too, observed, with the late Prof E Frank, 2 cases of deficiency of antihæmophilic globulin (A H G) (thromboplastinogen) with prolonged bleeding-time

CASE 1 —A thirteen-year-old girl had an entirely negative family history In childhood she had prolonged bleeding after minor cuts and bruised easily She had severe epistaxis The laboratory findings are summarised in the accompanying table

Test	Case 1	Case 2	Normal
Bleeding-time (min.)	60	8–11	2
Coagulation-time (min)	12–25	11	8
Prothrombin-time (Quick) (sec.)	12	12	12
Prothrombin-consumption time (Quick) (sec)	10	15	34
Thromboplastin-generation test (Biggs-Douglas)	Abnormal	Abnormal	Normal
T G T with normal $BaSO_4$-treated plasma (sec.)	8	9	
Subject's $BaSO_4$-treated plasma substituted in the normal system	Abnormal	Abnormal	
A.H.G (%)	5	8	80–120

A H G -deficiency was noted, and A H G was 5% The case was a pseudohæmophilia B (vascular hæmophilia or angiohæmophilia A) The cause of the prolonged bleeding-time was investigated and a platelet defect was observed under the electron microscope The aggregation and adhesiveness, the formation of pseudopodia, and the spreading of hyalomere of platelets were absent or defective [1] [2] (see fig)

CASE 2 —A year later, a second similar case (an eleven-year-old boy) was observed and the platelet defect was noted under the electron microscope [3]

Defective pseudopodia formation and lack of spreading of hyalomere of platelet in a case of A.H G -deficiency with prolonged bleeding-time (×15,000)

These findings suggest that in vascular hæmophilia besides A H G -deficiency there is a platelet defect as in the thrombasthenia described by Braunsteiner [4] and by ourselves [5] In other words, these cases are combinations of thrombasthenia and hæmophilia (thrombasthenia hæmophilica) In these cases, the so-called Frank's athrombia [6] [7] does exist—that is to say, the bleeding-time is prolonged because of defects in the aggregation and adhesiveness of platelets The same defect of platelets has been observed by Paykoç and Erişilgil [8] in a case of Christmas disease with prolonged bleeding-time This finding confirms our observations

In my opinion, the third and fourth cases of Professor Quick are examples of the syndrome of thrombasthenia hæmophilica or athrombia hæmophilica

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ORHAN NURI ULUTIN

DIPLOMA OF CHILD HEALTH

SIR,—In your educational number (Aug 30) you do not include the Royal Faculty of Physicians and Surgeons of Glasgow amongst those bodies which grant a diploma of child health Reference to the advertisement pages of the same number will confirm that it does

Royal Hospital for Sick Children,
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ROBERT A SHANKS

ACTION OF PSYCHOTROPIC DRUGS ON γ-AMINOBUTYRIC AND GLUTAMIC ACID IN RAT BRAIN

SIR,—Recently one of us (C de W) recorded [9] the results of an investigation into the inhibition of intermediary metabolism by some diphenhydramine derivatives Like the barbiturates, diphenhydramine reduces the oxygen consumption during oxidation of glucose (rat-brain slices) [10]

Generally speaking, the alkyl-substituted derivatives have a similar but more pronounced effect At the concentration used (0 002 M) the inhibition is antagonised by histamine Another remarkable effect is seen in the action of these compounds on aminoacid metabolism Paper chromatography showed that some of the compounds changed the level of at least two aminoacids which, to the best of our knowledge, were identified as glutamic acid and methionine Of the compounds investigated orphenadrine (β-dimethylaminoethyl 2-methylbenzhydrylether, 'Disipal'), gave the strongest effect—an elevenfold increase of glutamic acid and a more than seven-fold increase of "methionine" Orphenadrine, the pharmacological properties of which are quite different [11] from those of diphenhydramine, is used in the treatment of parkinsonism[12], but was recently found to have psychotropic activity[13] These observations suggested that it might be useful to investigate the influence of psychotropic drugs on the aminoacid metabolism

Using the "collidine" filter-paper technique of Dent [14] the influence of orphenadrine on the aminoacid spectrum was reinvestigated (substrate glucose 0 02 M, orphenadrine 0 002 M, buffer medium pH 7 2, weight of brain slices 80–100 mg) We were able to prove that the designation of one of the aminoacids mentioned above as "methionine" was incorrect, and that after the experiment γ-aminobutyric acid, as well as glutamic acid, was present in increased quantity

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[1] Frank, E., Ulutin, O N *Bull Soc. turq Méd* 1957, 23, 301
[2] Frank, E, Ulutin, O N, Pecikyan, R (in the press)
[3] Bilhan, N, Ulutin, O N, Karaca, M, Sestakof, D (in the press)
[4] Braunsteiner, H, Fellinger, K., Pakesch, F *Klin Wschr* 1953, 31, 21
[5] Akstas, S, Ulutin, O N *New Istan contr Clin Sci* 1954, 3, 22
[6] Frank, E, Ulutin, O N, Karaca, M *ibid* 1956, 4, 62
[7] Frank, E *Münch med Wschr* 1958, 100, 940
[8] Paykoç, Z, Erişilgil, O (unpublished observation)
[9] de Waart, C Thesis, Vrije Universiteit, Amsterdam, 1958
[10] de Waart, C *Acta physiol pharmacol Neerl* 1956, 5, 220, *ibid* 1958 (in the press)
[11] Bijlsma, U G, Harms, A F, Funcke, A B H, Tersteege, H M, Nauta, W T *Arch int Pharmacodyn* 1956, 106, 332
[12] Gillhespy R O, Ratcliffe, A H *Brit med J* 1955, ii, 352, Doshay, L J, Constable, K *J Amer med Ass* 1957, 163, 1352
[13] Scheurle, G *Dtsch med Wschr* 1957, 82, 2227
[14] Dent, C E *Biochem J* 1948, 43, 169

A preliminary investigation revealed that

(*a*) Psychotropic drugs inhibit oxygen consumption of metabolising brain slices from 0 to 89% (molar concentrations as above)

(*b*) If they affect aminoacid metabolism γ-aminobutyric acid and glutamic acid are involved, in some cases only glutamic acid is present in larger concentration after the experiment

The results so far are summarised in the accompanying table

INHIBITION OF OXYGEN CONSUMPTION AND INCREASE IN AMINOACIDS

Drug (0 002 M)	% inhibition	Aminoacid increase factor (normal value = 1)	
	O^{2} consumption	Glutamic acid	γ-aminobutyric acid
Chlorpromazine	89	7	10–20
Orphenadrine	59	7	10–20
Azacyclonol	36	4	1
Pipradrol	26	4	1
Benactyzine	25	3	1
Meprobamate	14	1	1
Adrenochrome (0 0005 M)	0	1	1
Deanol [15]	0	1	1

The inhibition of oxygen consumption by some psychotropic drugs is already known,[16] but it is not a specific property of these compounds As far as we know their influence on the aminoacid metabolism has not been investigated

During the past year γ-aminobutyric acid has attracted the attention of several investigators Its occurrence as free acid in relatively large amounts in the brain and its pharmacological actions—e g on central synapses—are very interesting [17]

We would not at the moment suggest that the action of some well-known psychotropic drugs could be explained by their influence on the γ-aminobutyric-acid and glutamic-acid level in the brain alone, but we think it useful to continue our investigations in this direction and into the possibility of a “ biochemical classification ” of psychotropic drugs

We are indebted to Mr W F Kafoe for his valuable help in the experiments

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W TH NAUTA
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C DE WAART
M J E ERNSTING

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[15] Pfeiffer, C C , Jenney, E H , Gallagher, W *Science*, 1957, 126, 610

[16] Bernsohn, J , Namajuska, I , Boshes, B *J Neurochem* 1956, 1, 145

[17] Purpura, D P , Girado, M , Grundfest, H *Science*, 1957, 125, 1200, Marrazzi, A S , Ross Hart, E , Rodriguez, J M *ibid* 1958, 127, 284, Roberts, E , Rothstein, M , Baxter, C F *Proc Soc exp Biol*, *N Y* 1958, 97, 796, Kuriaki, K , Yakushiji, T , Noro, T , Shimizu, T , Saji, S *Nature*, *Lond* 1958, 181, 1336

Public Health

Vaccination against Poliomyelitis

THE Minister of Health has issued details of the Government's plan for the extension of the poliomyelitis vaccination programme This plan, based on the recommendations of the Joint Committee on Poliomyelitis Vaccine, with Lord Cohen of Birkenhead as chairman, falls broadly into three phases

1 A drive to complete the vaccination of all those registered in the present priority groups and to raise the acceptance-rate among these groups as high as possible The present groups are (*a*) children aged 6 months to 15 years, (*b*) expectant mothers, (*c*) general practitioners, hospital staff in contact with poliomyelitis patients, ambulance staff, and the families of these groups

2 Vaccination of those born in 1933–42, thus raising the upper age limit from 15 to 25

3 Vaccination of a wider range of hospital staff—namely, all who come in contact with patients—and medical students and the families of these groups

4 Third injections It is suggested that these should be offered to all who have already had two, in approximately the same order in which they were given their earlier injections, and that an offer should be made as soon as possible to those who were vaccinated in 1956

Fluoridation

THE considered opinion of an international group of experts is given in a report from the World Health Organisation on the value of fluoridation of public water-supplies for the prevention of dental caries [1] This committee has no doubt about the efficacy, safety, or practicability of fluoridation it draws attention to the mass of evidence that concentrations of 1 p p m of fluorides, artificially or naturally present in drinking water, do no harm to health and go far to prevent decay of the teeth

Unfortunately many members of the public do not see fluoridation in terms of compensating for a deficiency they feel that something unnatural is being added, and they see possible danger to general health in drinking “ doctored ” water The importance of such opposition was shown recently by the local decision to discontinue fluoridation of the water-supply at Andover—one of the places which were participating in the Ministry of Health's test of the method At Andover, as in some towns in New Zealand, fluoridation had become an acute political issue, on which candidates in local elections were successful or defeated As the result of a series of elections, the scheme ceased to command a majority on the council and the original decision to cooperate was reversed [2]

The experience of New Zealand suggests that prejudiced opposition can be overcome by patient and vigorous instruction in the facts about fluoridation In a programme of this kind, publicity should be given to experiences of local natural fluoridation of public water-supplies, such as that at Deeping St James, in Kesteven, mentioned by the principal school medical officer for Lincolnshire in his annual report for 1957 In this area, the water has been naturally fluoridated at a constant level of 2 5 p p m for no less than twenty years, and, to quote the report, “ the markedly superior dental condition and oral hygiene of the children of Deeping St James provide striking evidence in favour of fluoridation of other water supplies ”

If the public could be convinced that countless people in these islands have been drinking naturally fluoridated water all their lives, with no ill effects, and that there is no essential difference between natural and artificial fluoridation, the opposition to this valuable preventive measure would at least be greatly weakened

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[1] Expert Committee on Water Fluoridation, 1st Report World Health Organisation Technical Report Series no 146 Geneva W H O 1958, pp 25 Obtainable from H M Stationery Office (P O Box 569, London, S E 1) 1*s* 9*d*

[2] See *Lancet*, July 26, 1958, p 204

Infectious Diseases in England and Wales

Disease	Week ended August				
	2	9	16	23	30*
Diphtheria	4	3	2	2	—
Dysentery	536	368	338	384	376
Encephalitis					
Infective	5	1	6	5	4
Post-infectious	6	2	3	4	1
Food-poisoning	261	173	287	226	397
Measles, excluding rubella	6307	5605	5102	3796	2810
Meningococcal infection	11	11	9	14	10
Ophthalmia neonatorum	32	21	16	36	21
Paratyphoid fever	9	5	5	4	4
Pneumonia, primary or influenzal	168	150	183	151	135
Poliomyelitis					
Paralytic	37	51	57	42	46
Non-paralytic	28	22	29	35	32
Puerperal pyrexia	202	186	237	198	214
Scarlet fever	555	410	373	326	286
Smallpox	—	—	—	—	—
Tuberculosis					
Respiratory	455	427	415	452	447
Meninges and C N S	8	6	10	12	3
Other	55	68	65	69	62
Typhoid fever	1	4	4	4	6
Whooping-cough	710	608	713	770	810

*Not including late returns

Obituary

RUPERT WATERHOUSE

M.D. Lond., F.R.C.P.

Dr Rupert Waterhouse, for many years a leading Bath consultant with special interests in rheumatology and clinical pathology, died on Sept. 1 at the age of 85.

A Yorkshireman, he was born at Sheffield, the youngest son of John Hodgson Waterhouse, M.D. He was a descendant of Sir Gilbert Waterhouse, surgeon to Sheffield Royal Infirmary, and grandson of John Hodgson, who practised surgery in Birmingham. He was educated in Sheffield at the Collegiate School and at Wesley College, and studied medicine at St. Bartholomew's Hospital, qualifying in 1897. In 1[illegible] he settled in Bath, where he ultimately became physician to the Royal United Hospital and the Royal National Hospital for Rheumatic Diseases, and, as his consultant practice spread, he was invited in turn to become visiting physician to the Victoria Hospital, Frome, and the cottage hospitals at Chippenham and Trowbridge. He was elected F.R.C.P. in 1929. He was a founder and past president of the Bath Clinical Society.

He served in the 1914-18 war first as a combatant in the North Somerset Yeomanry and later with the R.A.M.C. in Gallipoli, Egypt, Palestine, and France, and for two years he commanded the South West Mounted Brigade Field Ambulance before being gazetted to command the [illegible]th Southern General Hospital. During the second world war he returned from retirement to take the place of the pathologist to the Royal United Hospital, who was on active service.

During his later years, immediately before he left active practice in 1945, he practised mainly as a consultant in clinical pathology. His description of the clinical entity of acute suprarenal insufficiency from bilateral adrenal hæmorrhage (*Lancet*, 1911, i, 577) is well known to clinicians as the Waterhouse-Friderichsen syndrome. Of his retirement L. H. writes:

"During his later years Waterhouse was much handicapped by deafness and by an increasing lameness associated with osteoarthritis and Paget's disease of the hip. In spite of these disabilities, he was never known to complain, he retained his dry sense of humour and often mordant wit until the end, and he will be remembered as one of the great physicians of Bath and perhaps the finest after-dinner speaker of his time in the West Country. He was always more interested in the art and science of medicine and in research than in building a large consultant practice. He stood for all that was honourable in the practice of medicine and was bitterly critical of any form of showmanship or self-advertisement. A great reader, he was also a very fine bridge-player and, despite his physical disabilities, continued to play until the end."

Dr Waterhouse leaves a widow, a son, and a daughter.

Appointments

CUSACK, NORA, M.B. N.U.I., D.C.H., D.P.H.: senior assistant M.O. and school M.O., Castleford and Normanton, Yorkshire.

EVERED, L. J., M.R.C.S., D.M.R.D.: part-time consultant radiologist, Mansfield area hospitals, Nottinghamshire.

JACKSON, AGNES, M.B. Aberd.: assistant M.O.H., Ross and Cromarty.

LEVEAUX, V. M., M.B. Lond., M.R.C.P.: part-time consultant physician, Derby group of hospitals.

SANDLER, MERTON, M.B. Manc., M.R.C.P.: consultant chemical pathologist, Bernhard Baron memorial research laboratories, Queen Charlotte's Maternity Hospital, London.

Notes and News

PREVENTIVE MEDICINE IN ANCIENT PERU

THE Incas were an extraordinary people, and it is interesting to have the account of preventive and curative medicine among them which Sir Weldon Dalrymple-Champneys wrote after his visit to Peru and gave as his presidential address to the Royal Society of Medicine's historical section.[1] He points out that "though the curative side of the picture can be more or less matched in other cultures, the preventive side . . . was in many ways in advance not only of other contemporary civilizations, but of all throughout the world up to the end of the nineteenth century."

The Inca empire lasted from about A.D. 1000 to the Spanish conquest.

The Inca State, Sir Weldon says, "was one of the most benevolent despotisms the world has ever seen, and certainly one of the most efficient. The State saw to it that every subject, whatever his age, ability or health, had sufficient housing, nourishment, clothing, and amusement . . . security in marriage, freedom of worship, protection from special industrial hazards, freedom from debt (there was no money), security from oppression (the Inca sovereigns never abused their power or allowed others to do so), and protection from enemies outside. All these benefits were theirs, provided that they were never idle during working periods, stayed in their own provinces except when going up to the capital, Cuzco, for a feast, and did not break the laws. The Incas, in fact, gave their subjects a moral code far in advance of the peoples surrounding them. . . ."

Though they had no written language, they had a method of recording statistics, and possibly certain simple facts.

"The instrument used to record such statistics was the famous *quipu* (or *quipo*), a cord from which hung numerous knotted strings of different colours, the position of the knots indicating units, tens, hundreds and thousands. Men were specially trained to make the quipus and to interpret them and they are believed to have recorded not merely statistics, but even historical events.

"A census of the whole population of the empire was carried out every year, the population being divided into age groups. The accuracy of these statistics was safeguarded by severe sanctions, for the keeper of the records (called the *quipu-camayu*) who did not know what he should know, or who lied, was punished with death, 'without hope of reprieve' and the Indian who ran away to escape the census was poisoned. Special envoys of the Inca called the people together for numbering, even when they were in *articulo mortis*.

"Though labour was compulsory, the sovereigns took care that it did not exceed the power of the individual, and for this purpose account was taken of age, sex, health and the nature of the work in question. Never were governors more careful of the health of their people." The mining of mercury, which gives rise to "tremors and nervous spasms", was forbidden, and so was fishing for pearls. Only a small number of Indians were sent to the coca plantations, situated in hot and unhealthy country, and these workers were always inhabitants of hot districts. For very laborious tasks there was a rota system.

"TEACH YOURSELF"

SINCE the Teach Yourself books were started some twenty years ago, about 300 have been issued, and their range of subjects is now astonishing. To celebrate the beginning of the 21st year there is now "A Concise Guide to Teach Yourself",[2] which in the words of Mr. Leonard Cutts, the editor, "is meant to introduce you, as agreeably as possible, to the infinite variety of knowledge, the endless things you could learn, and make, and do if life were only long enough."

In his foreword Mr. Ritchie Calder compares the series to the clandestine teaching movement, called "the Floating University", which flourished in Poland under the Czars. At any rate, he feels, the fact that the sale of these books runs into many millions suggests that "perhaps one is wrong in saying that we are becoming a nation of listeners-in and lookers-on." The authors include many whose names are widely respected, and Mr. Calder tells with relish the story of an undergraduate who scornfully rejected his advice to read one of the books—until he found that it was by his own professor.

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[1] *Proc. R. Soc. Med.* 1958, 51, 385.

[2] London: English Universities Press, 102, Newgate Street, E.C.1. 1958. Pp. 196. 2s.

SURVIVAL AFTER SHIPWRECK

In the world wars a high proportion of the deaths at sea were caused by drowning and exposure Between shipwreck and rescue survivors need buoyancy and nutrition, and details of experimental studies and of the equipment and procedures adopted by the Admiralty can now be seen on film

The Flotation Properties of Life-Jackets (16mm , silent, black-and-white, 12 minutes, Britain, 1945)[1] is a fascinating record of an investigation to discover whether a life-jacket lifted the head of an unconscious person out of the water Prof E A Pask, wearing a life-jacket, was anæsthetised by Sir Robert Macintosh and dropped repeatedly into a swimming-bath and a rough-water tank The efficacy of the jacket is well shown in the film from both above and below water at normal speed and in slow-motion

Survival at Sea (16mm , silent, black-and-white, 25 minutes, Britain, 1950–53)[2] shows a series of experiments conducted by the Department of Experimental Medicine, University of Cambridge, with various types of emergency rafts Investigations included conditions encountered in moderate, arctic, and tropical climates

Survival at Sea,[3] a recent film made by the Admiralty, shows in detail the equipment now used in the Royal Navy and the routine to be adopted by survivors Part I "Equipment" (16 and 35 mm , sound, black-and-white, 20 minutes, Britain, 1956) begins with a demonstration of the inflation and maintenance of a life-jacket, and then the inflatable life-raft and its associated survival-pack are described in detail The second half of the film is devoted to an exercise in which a raft is inflated and boarded The importance of maintaining body-fluid is emphasised, and accordingly fresh water and a plentiful supply of anti-seasickness tablets are provided Facilities for collecting rain water and a "solar still" are supplied Part II "Living on Air" (16 and 35 mm , sound, black-and-white, 32 minutes, Britain, 1957) is a dramatised account of life in a raft pending rescue Duties are allocated, and an inventory check showing the position of all the items in the raft and in the survival pack is carried out Boredom is relieved by a pack of cards and a comprehensive instruction book detailing the routine duties—times for issuing rations and so on Each man is given one pint of water daily to be drunk in the evening, next morning, and the remainder at midday Sufficient water for five days is provided, and as none should be consumed on the first day the survivors should be in good condition for six days Glucose sweets complete the rations The photography, all in sunny Mediterranean weather, is excellent

Royal Faculty of Physicians and Surgeons, Glasgow

On Aug 29 Prof Stanley Alstead, the president, conferred honorary fellowships on Sir Alexander Fleck, Sir Maurice Bloch, Prof Carl Browning, and Mrs Stirling of Keir

On Sept 1 the following were admitted to the fellowship

Sukumar Mukherjee, Raojabhai Ranchodbhai Patel, T F Rodger, George Rutledge, Thomas Symington

British Institute of Radiology

This institute will hold a meeting at 32, Welbeck Street, London, W 1, on Friday, Oct 17, when short papers on work in progress in radiobiology will be read

Committee on Artificial Insemination

The Government have now announced the names of the committee which, under the chairmanship of Lord Feversham, is to inquire into the practice of human artificial insemination and its legal consequences The members are

Dr L Priscilla FitzGibbon, anæsthetist to a group of Gloucestershire hospitals and a juvenile court magistrate, Mrs Peggy Jay, wife of Mr Douglas Jay, M P for Battersea North, and a member of London County Council, Dr D T McDonald, a general practitioner, Belford, Northumberland, Mr Ralph Risk, president of the Law Society of Scotland, 1957–58, Mr John Ross, formerly head of the Children's Department, Home Office, and chairman of the Marriage Guidance Training Board, Mr Justice Stevenson, Q C , a High Court judge, Dr R E Tunbridge, professor of medicine, University of Leeds, and Mrs H Whitley, wife of the minister of St. Giles' Catherdral, Edinburgh

The secretary of the committee is Mr R F D Shuffrey, Home Office, Whitehall, London, S W 1

University College, Ibadan

Mr W W Davey has been appointed to the chair of surgery

Mr Davey graduated M B from Queen's University, Belfast, in 1935, and after holding demonstratorships there in physiology and anatomy took the F R C S I in 1941 For the next five years he served with the R A F Medical Service, and he landed in Normandy on D-day with a surgical team In 1946 he was appointed chief surgical assistant to the gastroenterological unit at St James's Hospital, Balham In 1949 he took the F R C S , and the following year he took up his present consultant appointment as gastroenterological surgeon to Whittington Hospital and New End Hospital, London He gave a Hunterian lecture at the Royal College of Surgeons of England last year, and his published work includes papers on partial gastrectomy for peptic ulcer in the aged and on Rovsing's sign

Dr G M Edington has been appointed to the chair of pathology

Dr Edington graduated M B from the University of Glasgow in 1935, and after holding a resident appointment at Stobhill Hospital he joined the R A M C and served in India and Burma He was demobilised with the rank of major in 1946 and soon afterwards joined the Colonial Service He served at first as a pathologist in the Gold Coast (now Ghana), and in 1947 he took the D T M H In 1951 he took the D C P , and in 1953 he obtained his M D with high commendation The following year he was appointed specialist pathologist in charge of the medical research institute and laboratory services of the Gold Coast In 1957 he returned to this country to take up his present post of consultant pathologist to Whiston and Rainhill Hospitals in the Liverpool region This year he was appointed M B E in recognition of his services in Ghana. His published work includes papers on sickling and on abnormal hæmoglobin diseases

The Privy Council has recognised the clinical facilities at University College Hospital, Ibadan, for the purpose of the degrees of M B , B S , of the University of London for an initial period of three years

St Luke's Day Service

A service for doctors is to be held at All Souls' Church, Langham Place, London, W 1, at 11 A M on Sunday, Oct 19 Lord Moran and Sir Cecil Wakeley will read the lessons

Seats will be reserved for doctors and their families Application (stating the number of tickets required) should be made to the church secretary at All Souls' Church by Oct 16

Institute of Directors

This institute has set up a medical research unit to inquire into the health problems of directors The director in charge of the unit is Dr H Beric Wright, F R C S , formerly on the staff of the Shell Group

On Friday, Oct 3, at 3 P M , Prof Dorothy Russell will give the inaugural address to the Royal Free Hospital School of Medicine, Hunter Street, London, W C 1

On Monday, Oct 6, at 3 P M , Sir Christopher Hinton will give the inaugural address to the Westminster Medical School at Church House, Great Smith Street, London, S W 1

A conference of surgeons of the St John Ambulance Brigade will be held at the B M A House, London, W C 1, on Nov 1 and 2

Group-Captain H P R Smith has been appointed president of the central medical board and adviser in aviation physiology at the central medical establishment of the Royal Air Force

The Friends of Blandford Hospital have opened a fund to provide a memorial to the late Dr W H C Spooner at the hospital Donations should be sent to the treasurer, 6, West Street, Blandford

The Hand Club of Great Britain and the Second Hand Club are meeting at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W C 2, on Saturday, Nov 22, from 10 A M Further particulars may be had from Mr H Graham Stack, hon secretary of the Second Hand Club, at 150, Harley Street, W 1

The annual dinner of the Sheffield Medical School Old Students' Association will be held in the Firth Hall of the university on Saturday, Oct 11, at 7 P M Further particulars may be had from Dr J D H Linfoot, department of pathology, Western Bank, Sheffield, 10

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[1] Available from Sir Robert Macintosh, F F A R C S , Radcliffe Infirmary, Oxford

[2] Available on hire from the British Film Institute, 4, Great Russell Street, London W 1

[3] Available on hire or sale from the Director of Stores (10c), Admiralty, Whitehall, London, S W 1 (Catalogue no A635)

The Lancet · Saturday 20 September 1958

MALIGNANT DISEASE OF THE URINARY TRACT*

Sir Eric Riches
M.C, M S Lond, F.R C S
SURGEON AND UROLOGIST, THE MIDDLESEX HOSPITAL, LONDON, W 1

THE URETHRA

In the discussion of carcinoma of the bladder stress was laid on the different behaviour of papillary and solid growths In malignant growths of the urethra there is a similar duplicity of behaviour, but it depends more upon the situation of the tumour than on its histological structure

Seven years ago Cullen and I reported 34 cases of urethral carcinoma (Riches and Cullen 1951), to those I can now add another

The tumours fell into two groups, anterior and posterior, and there was evidence in some that the urethral growth was an implant from the bladder Invasion of the inguinal glands had occurred in half and distant metastases in about a third

Prognosis

There is a striking difference between the prognosis of the anterior and the posterior growths

Only 2 out of the 9 patients with growths of the anterior urethra lived for *less* than three years the remainder all passed the five-year mark Only 2 patients had metastases, and 1 of these, whose inguinal glands were irradiated, is alive and well seven years later By contrast, with tumours of the deep urethra the outlook is very bad 19 out of 20 patients were dead within four years and 14 had metastases

The increased liability to metastases is one of the reasons for the poor prognosis of deep tumours Other factors are the lateness of the symptoms and failure to recognise them at a curable stage In addition, the deep urethra is less accessible to treatment than the anterior part, and one may be reluctant to carry out a sufficiently radical extirpation for what appears to be a small localised tumour

Treatment

For anterior urethral cancer in the male the best treatment is partial amputation of the penis If radiotherapy is given in adequate dosage, the growth may be followed by stricture In women diathermy excision followed by irradiation, either by radium implantation or by X rays, is satisfactory In either sex suspicious glands in the groin should be subjected to biopsy, and, if invaded, treated by X rays or by block dissection

For the vulvourethral growths in women wide excision with urinary diversion offers some hope, but they are generally better treated by irradiation with radium needles or applicators Men with carcinoma of the bulbomembranous urethra often come too late for effective treatment. The story of a stricture, of periurethral and later perineal suppuration and of nodules in the skin with invaded inguinal glands, is characteristic Irradiation at this stage makes the infection worse but I believe that a combination of well-timed radiotherapy and of surgery is still our best weapon

Extension or implantation of a bladder growth into the urethra worsens the outlook it lays the inguinal glands open to invasion and it promotes distant metastases The urethral tumour may be discontinuous with the main growth, when it can be removed by a separate operation, but even a discrete papillary carcinoma of low malignancy will sometimes invade the inguinal glands It would appear that confinement to the narrow tubular urethra encourages growth into the deeper tissues, whilst in the more spacious bladder there is room for surface expansion

THE PENIS

Carcinoma of the penis is not common Of 24 patients with malignant penile growths the youngest was thirty-two and the oldest eighty-three The average age was sixty-one There were only 17 admissions to the Middlesex Hospital in five years

It is well known that the disease is exceedingly rare in those circumcised in infancy, and phimosis and its consequent lack of cleanliness are undoubtedly predisposing factors I do not advocate universal circumcision, but if the pædiatricians who condemn the operation saw some of the patients later in life they might reconsider their attitude

Types

Although it is one of the least malignant of the growths of the urinary tract, carcinoma of the penis obeys the rule and occurs in two main forms The *papillary* type grows slowly into a large cauliflower-like excrescence with surface ulceration Glands in the groin are enlarged by sepsis but rarely invaded by growth The total removal of the organ can be followed by cure The *ulcerative* type may be small, but it grows by infiltration of the underlying tissues, invasion of the inguinal glands, and sometimes by bloodborne spread through the cavernous spaces A man with this lesion may be dead within two years Thus, as in the bladder, the larger growths are often less malignant.

There are other types of which the intraepidermal carcinoma —known variously as Paget's disease, Bowen's disease, or erythroplasia of Queyrat—is considered to be precancerous At an early stage it can be cured by X-ray therapy leaving a presentable member

Treatment

Both surgery and irradiation have a part to play in treatment Irradiation alone, either by X rays or by radium, will sometimes cure a small lesion, but the need for amputation after irradiation arose in 5 out of 8 cases There is a natural desire to preserve the penis, and a patient may prefer a distorted member to none at all In 3 patients a local excision only was done, and 1 of them has survived five years without recurrence The other 2 are living after shorter periods The more usual surgical treatment is partial amputation, this was the choice in more than half the patients The need for total amputation is determined by the extent of the lesion, when the penis is almost completely destroyed, partial amputation is impossible I no longer do the radical amputation but prefer biopsy of the inguinal glands at the time of the total or partial amputation, dealing with them subsequently if necessary When the glands are invaded, irradiation should be the primary treatment,

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* Based on the second of three Lettsomian lectures for 1958 delivered before the Medical Society of London

TABLE I—RESULTS OF TREATMENT IN CARCINOMA OF PENIS

5-year survivals	13/13 (*100%*)
10-year survivals	2/4 (*50%*)
Died from the disease	1 at 2 years*
Died from other causes, without recurrence	4 { 1 at 8 years 1 at 7 years 2 at 6 years

*Operated upon in 1954 and therefore not yet a possible 5-year survivor

but the need for a possible subsequent block dissection should be borne in mind

After treatment of the glands, by whatever method, there is a tendency to œdema of the legs This can persist for many months The ingenious rotation flap devised by Lee (1955) may overcome the tendency to non-union of the skin, but it adds considerably to the operation The other complication is meatal stenosis This occurs almost exclusively after partial amputation, and especially when irradiation has been given before operation It can be avoided by removing a disc of skin of the lower flap and by passing the urethra through this rather than through a stab wound A $^1/_2$-inch projection of urethra looks ugly at the time, but eventually it leaves a rosette of mucosa with no constriction

Cancer of the penis is the only carcinoma in the urinary tract which can boast a 100% five-year survival-rate (table I) (Savage 1957) Nevertheless, the 1 death in my series was from widespread pelvic deposits with compression of one ureter The ulcerative type can show its truly malignant nature

In partial amputation conservatism in the length of stump is desirable as sexual function may be preserved On the other hand, I believe that total amputation should include removal of the testicles

THE SCROTUM

Carcinoma of the scrotum is a dying disease which was formerly prevalent amongst chimney-sweeps, tar workers, gas workers, coalminers, and mule-spinners During 1936–39 only 4 cases were admitted to the Middlesex Hospital, and there have been none since

The primary growth should be treated by wide excision Invaded inguinal lymph-glands may be removed by block-dissection, followed if necessary by irradiation After irradiation the tissues in this region are devitalised and subsequent surgery is fraught with a grave danger of infection The danger appears greater in scrotal than in penile cancers, although it exists in both

THE PROSTATE

The prostate is the commonest site of malignant disease in the urinary tract and it accounts for about 10% of all cancers in men It is encountered in three main forms Firstly, there is the patient in whom the diagnosis is certain from the hard, irregular, fixed, infiltrating tumour felt on rectal examination Secondly, there is the latent or unsuspected carcinoma which has all the signs of benign hyperplasia but in which an area of carcinoma is found on histological examination after prostatectomy Thirdly, the occult form may be present in the patient who comes complaining of lumbago or sciatica without urinary symptoms He is often found to have widespread metastases

Diagnostic Aids

The serum-acid-phosphatase level is raised in some 80% of patients with metastases, and a figure of 10 King-Armstrong units is diagnostic of metastatic prostatic carcinoma With bone metastases the serum alkaline phosphatase is also raised, but this is not specific for prostatic tumours The administration of œstrogens will lower these figures if therefore the test is to be of help in diagnosis, blood must be taken before treatment is started

A prostatic biopsy can be performed by the transurethral route, with a needle through the perineum, or by open perineal excision Transrectal biopsy is also used in some centres A positive result is diagnostic, but in an early case it is difficult to remove the right nodule False negatives are not uncommon I have been somewhat disappointed by the results of immediate section at the time of operation, more than once the clinical impression of malignancy was more accurate than the histological picture given by rapid staining

The recent science of exfoliative cytology has also been used as a diagnostic aid In the examination of the fluid expressed by prostatic massage the experience of the pathologist is of paramount importance The diagnostic opinions of Prof J Bamforth, who has examined the secretion from many of my patients, have been of very great value Despite these modern aids, however, diagnosis still rests on the result of a careful rectal examination Early detection is the only way in which cases suitable for radical prostatectomy with a prospect of complete cure can be found

Treatment

Surgical

The theoretically ideal form of surgery is total prostatectomy, including removal of the prostatic capsule, the seminal vesicles, and the base of the bladder Because of early infiltration this ideal is attainable in only about 5–10% of cases In some American clinics a higher operability-rate is claimed, and this is used to encourage the routine annual rectal examination of all men over forty Whether this form of control will ever be accepted here is open to doubt

Radical prostatectomy can be done by the retropubic or the perineal route Its chief disadvantage is its liability to be followed by urinary incontinence its chief merit is a high potential cure-rate Kimborough (1956) reported the five-year survival of 36 out of 56 patients so treated

Simple prostatectomy by the retropubic, suprapubic, or perineal route will not completely remove the clinically manifest malignant prostate Sometimes digital removal of such glands is impossible, but usually they can be excised with diathermy For such cases, however, which almost break the surgeon's finger, transurethral resection offers a good alternative, provided the instrument can be introduced and provided enough tissue can be removed to relieve the obstruction For latent carcinomas open prostatectomy has the advantage over transurethral resection in that complete removal of the malignant areas is more likely Where there is reasonable doubt about the diagnosis I prefer the retropubic operation to transurethral resection A preliminary course of stilbœstrol sometimes makes the operation easier

The frequent origin of cancer in the posterior lobe or in the peripheral zone of the gland makes it imperative to remove the posterior capsule, rather than to enucleate the adenoma, in all prostatectomies After enucleation of a histologically benign adenoma recurrence as a prostatic carcinoma is not unknown I have records of 10 such cases

After enucleation of the gland I now excise the posterior capsule with the diathermy needle, the trigonectomy is continued downwards with the sheet of tissue covering the seminal vesicles The seminal vesicles are removed too if they are adherent This part is examined separately In a recent case the prostate showed benign hypertrophy, whilst the posterior lobe and its capsule contained infiltrating adenocarcinoma

Hormone Control

Stimulation of the prostate by androgens can be reduced by castration or by giving œstrogens Nesbit and Baum (1950) collected statistics of about a thousand cases treated by one or other method alone, and by the two together, comparing them with a control group of untreated patients The figures showed the longest survival in patients under the combined treatment with castration and œstrogens

Castration sounds abhorrent, but the operation is one of subcapsular orchidectomy which leaves something in the scrotum that is scarcely distinguishable from the atrophied testes resulting from œstrogens The patient is told that the operation will alter the secretion of the testicle It has many advantages for the man who cannot or will not take œstrogen or who forgets to do so It also allows a lower dosage with consequent lessened side-effects I believe that it should be an essential part of the treatment of every carcinoma of the prostate except in the latent cases with a small central area of cancer

Œstrogens act by inhibiting pituitary gonadotrophin which stimulates the testes It has been claimed recently that stilbœstrol has a local cytostatic effect as well, and in its phosphorylated form (' Honvan ') it is said to have an enhanced therapeutic action when given intravenously (Hasche-Klunder and Wilmanns 1957) In a trial on a few cases I have not found such an improvement, and the serum acid phosphatase has tended to rise rather than to fall, at least in the advanced cases ' Tace ', another proprietary œstrogen, is said to be stored in the fat and to give less troublesome side-effects

The initial dose of stilbœstrol may be as small as 3 mg a day, increasing to 15 mg a day, although Fergusson and Franks (1953) have shown that 100 mg is equally well tolerated and more effective I agree that this is so, but I prefer to withhold higher doses until a clinical failure to respond demands them. A maintenance dose is required indefinitely many patients have relapsed because the drug has been discontinued owing to an apparent " cure "

The common side-effects of stilbœstrol—testicular atrophy, impotence, breast changes—can be disquieting to the patient, but they are seldom severe enough to warrant discontinuance of treatment Of more serious import is the occasional case of fluid retention with œdema, some men with cardiac disease are forced to abandon the drug Again orchidectomy provides the alternative

Cortisone, which inhibits the production of adrenocorticotrophic hormone by the pituitary, has a place in treatment in some patients it will relieve the pain of bone metastases

Adrenalectomy and Hypophysectomy

Enlargement of the adrenals with an increased production of androgens may follow testicular atrophy, but the effects of bilateral adrenalectomy are not so dramatic as in carcinoma of the breast Scott (1956) states that it should be considered only if the patient has androgen metabolites in the urine whilst on a dose of 100 mg of cortisone daily

Methods of destruction of the pituitary by irradiation, ablation, or division of its stalk are on trial No large series of results has yet been reported

Irradiation

X-ray therapy was a useful ancillary method before the days of stilbœstrol and we are starting to use it again in patients with bony metastases Prostatic injections of radioactive colloidal gold have also been tried, but there is a danger of producing severe proctitis Most of the gold, moreover, escapes into the blood-stream during the first few minutes, into the urine during the first few hours, and into the lymphatics within the first few days (Kerr et al 1957)

Results

The prognosis of cancer of the prostate before the days of hormone control depended largely on its spread, on its degree of malignancy, and on the amount of urinary obstruction and renal damage it was causing In 1943 in a series of 70 patients treated by transurethral resection and X rays, I found an average duration of life in clinically manifest cases of nearly two years, 1 patient lived for five years In latent or unsuspected cases, treated by prostatectomy and X-ray therapy, the average survival was three years, 1 patient living for nearly ten years The advent of hormone control has brought about a remarkable change Although no patient can be said to have been completely cured, length of survival, relief of urinary obstruction, and the ability to lead an active life with freedom from pain are all greatly increased

I have not attempted to estimate percentage survivals the time from first symptoms to first treatment is too variable and the final follow-up not sufficiently complete I have, however, examined the records of 200 patients with a complete follow-up (table II), excluding those who had a malignant recurrence after simple prostatectomy The oldest patient was ninety-two, the youngest forty-five, their average age was sixty-eight 12 were over eighty when first seen

TABLE II—SURVIVAL IN 200 CASES OF CARCINOMA OF PROSTATE

Less than 1 year	40
More than 3 years	93
" " 4 "	75
" " 5 "	53
" " 7 "	31
" " 10 "	10

In considering the long survivors we must separate those who had a small central area of carcinoma in an otherwise benign prostate This was so in 3 of the ten-year survivors and 5 of those who lived for seven years

One man of seventy-three with such a latent growth developed a local recurrence in the prostatic urethra five years after prostatectomy For the next five years he took stilbœstrol, and he remained well until his death at eighty-three In several the growth was histologically of low-grade malignancy or of limited extent, but in some it was extensive One medical man had a hard fixed malignant prostate at the age of sixty-two Transurethral resection of 11 g prostatic tissue relieved his obstruction The gland showed extensive invasive adenocarcinoma He has had stilbœstrol, 5 mg daily, ever since, and he is alive and well twelve years later His serum acid phosphatase was never raised.

At the other end of the scale are the patients who have widespread osseous or lymphatic metastases when first seen, usually with a raised serum acid phosphatase There were 51 who had such metastases before treatment was started (table III) Multiple secondaries in the lungs

TABLE III—SURVIVAL IN 51 CASES OF CARCINOMA OF PROSTATE WITH METASTASES

Less than 1 year	11
More than 1 year	40
" " 2 "	34
" " 3 "	18
" " 4 "	12
" " 5 "	9
" " 7 "	4
" " 8 "	2

not infrequently disappear on treatment with œstrogens. *Bone metastases* regress more slowly and the changes are more apparent in the less common osteolytic deposits which may show recalcification Metastases in palpable lymph glands can disappear quite quickly As a rule a high serum acid phosphatase denotes a bad prognosis Its fall indicates a good response and new metastases produce a rise

Subcapsular orchidectomy was done in 68 of the 200 patients It is now our policy to use it more extensively Half the patients still alive and only a quarter of those who died had had orchidectomy The prognosis appears to be better in older patients, but I think the real explanation of this lies in a lower grade of malignancy The average survival of the 12 octogenarians was two years and four months

Conclusion

Prostatic carcinoma differs from the disease in other parts of the urinary tract in being influenced and controlled by naturally occurring hormones It is the first form of cancer to respond to treatment by oral medication, let us hope that there will soon be others

REFERENCES

Fergusson, J D , Franks, L M (1953) *Brit J Surg* 40, 422
Hasche-Klunder, R , Wilmanns, H (1957) *Brit J Urol* 29, 20
Kerr, W K , MacDonald, J C F , Smythe, C A , Comet, V (1957) *Canad J Surg* 1, 63
Kimborough, J C (1956) *J Urol* 76, 287
Lee, E S (1955) *Lancet*, ii, 520
Nesbit, R M , Baum, W C (1950) *J Amer Med Ass* 143, 1317
Riches, E W (1943) *J Fac Radiol* 16, 187
— Cullen, T H (1951) *Brit J Urol* 23, 209
Savage, C R (1957) *ibid* 29, 69
Scott, W W (1956-57) Year Book of Urology Chicago

COMPARISON OF ANIMAL AND VEGETABLE FATS IN INCREASING BLOOD COAGULABILITY

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WE have shown previously that, after the ingestion of a meal of high animal-fat content, there occurs a shortening of the "accelerated clotting-time" (using plasma and Russell-viper venom) and of the clotting-time of whole blood in silicone-coated tubes (Fullerton et al 1953) An increase in coagulability after a high-fat meal has been found by other workers (O'Brien 1956, 1958, Keys et al 1957, Pilkington 1957) More recently, attempts have been made to determine whether this effect occurs equally after the ingestion of animal and vegetable fat Unfortunately, published reports have been conflicting, and a study of these reports does not provide an obvious explanation for the variation in results For example, O'Brien (1956), using the "accelerated clotting-time" *with Russell-viper venom and platelet-poor* plasma, found similar degrees of shortening after the ingestion of 50 g butter, 50 g margarine, and two eggs On the other hand, Maclagan and Billimoria (1956) found a shortening of the "venom-time" after ingestion of 2 oz butter, but not after the same amount of margarine In addition they found that the "calcium-times" (method of Biggs and Macfarlane 1953) agreed with the "venom-times"—shortening after feeding butter but not margarine

TABLE I—SIMULTANEOUS R P C TIMES (SEC) IN BOTH ARMS (N DIFFICULTY IN VENEPUNCTURE)

Rt arm	Lt arm	Difference
125	111	14
117	112	5
129	123	6
108	114	6
109	112	3
108	110	2
92	89	3
105	105	0
103	101	2
122	123	1
96	98	2
100	99	1
95	98	3
88	90	2
91	94	3
		Mean 3 5

When these reports appeared we had already carried out a series of experiments which showed that ingestion of vegetable fat usually produced a shortening of the recalcified-plasma clotting-time of the same order as that which follows a meal of bacon, eggs, and butter In view of the discrepancy between the findings of O'Brien and those of Maclagan and Billimoria, we extended our experiments in the hope of finding the reason for their conflicting conclusions The issue appeared to us to be important since we have already adduced evidence to suggest that one factor related to the increasing incidence of cardiac infarction may be the increase in dietary fat (Fullerton 1955) Moreover the increase of dietary fat in this country in the past few decades has been due mainly to a greater intake of vegetable fat (Fullerton 1956)

Methods

All blood samples were obtained by dry-sterilised 5 ml syringes (all-glass 'Vim') and needles (19 B W G 1 in), separate syringes and needles being used for each blood sample Venepuncture was carried out as carefully as possible to reduce tissue trauma to a minimum, and a note was made if any difficulty was encountered in entering a vein 4 5 ml of blood was withdrawn and added to a tube containing 0 5 ml 1 34% sodium-oxalate solution The tube was inverted two or three times to ensure mixing and was then spun for 5 minutes at 2000 r p m The recalcified-plasma clotting (R P C) time was estimated by adding 0 2 ml *M*/50 calcium chloride solution to 0 2 ml of plasma in a glass tube (3 in x 3/8 in.) in a water-bath at 37°C The tube was gently tilted at intervals, and the end point was taken as the first definite appearance of fibrin threads All estimations were made in duplicate All the steps in this technique were undertaken by one of us (G A M), and the interval between withdrawal of blood and estimation of R P C time varied very little and was approximately half an hour

The method was found to give very consistent results The difference between duplicate readings in no instance exceeded 7 seconds, and averaged 2 2 seconds As a further check on the reliability of the technique, blood samples were obtained from veins at both elbows at the same time in 19 subjects Table I shows the results in 15 patients in whom no difficulty in venepuncture was encountered With 1 exception (case 1) the greatest difference between the two arms was 6 seconds In the other 4 subjects (see table II) difficulty in venepuncture at one elbow was unavoidable in the first two instances The R P C times on that side were 28 and 14 seconds less than on

TABLE II—SIMULTANEOUS R P C TIMES (SEC) IN BOTH ARMS (VENEPUNCTURE DIFFICULT IN RT ARM)

Rt arm	Lt arm	Difference
75	103	28
110	124	14
115	130	15
73	87	14
		Mean 17 8

the other In the remaining 2 subjects venepuncture at the right elbow was deliberately preceded by slight tissue trauma by the entering needle The R P C times on that side were 15 and 14 seconds less than on the other

The R.P C time was used as an index of blood coagulability in preference to the "accelerated clotting-time" using Russ viper venom and the clotting-time of whole blood in silico- coated tubes It has the advantage that no foreign throm plastin is added as in the venom test, and the techniq simpler than the use of silicone-coated tubes We have ever, found that all three methods show an acceleratio clotting during the phase of lipæmia after ingestion of a fat meal

Convalescent-ward patients, aged 20–61, with no hist cardiac disability, were selected as subjects After a samp venous blood had been obtained from the subjects in the f state, they ate one of the following meals

1 *Animal-fat breakfast* —2 eggs, 2½ oz bacon, 1–1½ oz bread, and tea with milk and sugar Fat content approximatel

2 *Vegetable-fat breakfast* —2 fishcakes fried in margarine with margarine, 1 oz walnuts (in shells), tea with milk and Fat content approximately 83 g (walnuts 14 6 g, mar 68 7 g)

The margarine used in the earlier experiments contained a amount of hydrogenated marine oil in addition to palm-kern palm-oil, and groundnut oil In later experiments we used a garine made specially for us which contained only coconut oi groundnut oil No significant difference in the results was when the type of margarine was changed The addition of wa to the vegetable-fat meal was made at the suggestion of the die who prepared it, she felt that patients would have had difficu consuming it if the total fat content had consisted of margarine

Blood samples were obtained at 3 and 4 hours after inge of the meal

Results

Table III summarises the results in 11 subjects wh one day took the high-fat meal containing bacon, but and eggs, and on another day the meal high in vegetable fat In general there is little difference between the readings at 3 and 4 hours In all 11 subjects the animal-fat meal was followed by significant shortening of the R P C time, at 3 hours this reduction varied from 28 to 66 seconds with a mean of 38 7 seconds, at 4 hours the range was from 24 to 73 seconds with a mean of 35 5 seconds No difficulty in venepuncture was encountered in this series of experiments

TABLE III—R P C TIMES (SEC) BEFORE AND AFTER HIGH-FAT MEAL

Subject	Animal fat			Vegetable fat		
	Fasting	3 hr	4 hr	Fasting	3 hr	4 hr
1	121	76	84	119	85	94
2	114	86	82	121	77	8[illegible]
3	132	99	96	138	102	101
4	116	68	74	139	87	83
5	96	65	64	100	95	98
6	109	80	77	101	88	99
7	105	75	76	105	82	86
8	122	74	98	119	84	100
9	103	70	76	113	72	88
10	126	60	53	119	62	50
11	111	76	85	120	68	84
Means	114	75	79	118	82	88

After ingestion of the vegetable-fat meal, no significant shortening occurred in 1 subject (5), in this case difficulty was experienced in entering veins, and this may explain the unexpected result The reduction in another subject (6) was of doubtful significance (13 seconds) at 3 hours, and only 2 seconds at 4 hours, and there is no obvious explanation for this result In the other 9 subjects the reductions in the R.P C times were of the same order as those found after the high animal-fat meal, at 3 hours the range was from 23 to 57 seconds (mean 41 6 seconds), and for all 11 subjects the mean reduction was 35 6 seconds, at 4 hours the range was 19–69 seconds (mean 35 9 seconds), with a mean reduction for all 11 subjects of 29 7 seconds

TABLE IV—R P C TIMES (SEC.) BEFORE AND AFTER 50 G AND 30 G VEGETABLE FAT

Subject	50 g			30 g		
	Fasting	3 hr	4 hr	Fasting	3 hr	4 hr
1	111	65	79	101	94	87
2	92	63	79	95	89	81
3	81	60	72	78	64	61
4	96	75	67	87	66	53
5	85	75	82	95	77	69
6	130	109	124	133	124	129
7	129	111	125	131	123	129
8	129	118	117	136	129	131
9	139	119	119	146	131	134
10	130	114	100	141	130	118
Means	112 2	90 9	96 4	114 3	102 7	99 2

These observations have been extended by measuring the R P C times in the fasting state and at 3 and 4 hours after 50 g and 30 g vegetable fat in 10 additional subjects The findings are presented in table IV In this series of experiments the special margarine referred to above (coconut oil and groundnut oil) was the only fat given At 3 hours after 50 g vegetable fat the reductions in R P C times varied from 10 to 46 seconds with a mean of 21 3 seconds, and at 4 hours the shortening of the R P C times showed a range of 3 to 32 seconds with a mean of 15 8 seconds When the fat intake was 30 g the mean reduction of R P C times was 11 6 seconds (range 6–21 seconds) at 3 hours and 15 1 seconds (range 2–34 seconds) at 4 hours Accordingly the reductions in R.P C times at 3 hours after the ingestion of vegetable fat are proportional to the amount ingested (intake 83 g, mean reduction 35 6 seconds, intake 50 g, mean reduction 21 3 seconds, intake 30 g, mean reduction 11 6 seconds), at 4 hours the difference between 50 and 30 g of fat is not significant

Discussion

The results demonstrate clearly that the R P C time shows a similar reduction after the ingestion of animal and vegetable fat when the amount ingested is approximately 85 g When the intake of vegetable fat is reduced the shortening of the R P C time is less pronounced In view of the discrepancies in the results of other workers we have paid particular attention to technique, and we are satisfied that, in our hands, the R P C test gives accurate and reproducible results if no difficulty in venepuncture is encountered We have been unable to discover a satisfactory explanation for the failure of some workers to find a shortening after the ingestion of vegetable fat

It seems reasonable to suggest that, since alimentary lipæmia accelerates the clotting of blood in vitro, it may lead to increased fibrin formation in vivo and so initiate and accelerate the development of atherosclerosis Our results show that, if this hypothesis is correct, animal and vegetable fats of the types used in our experiments are likely to have the same influence on the development of this process

Summary

The clotting-time of recalcified plasma is a satisfactory measure of the increase in coagulability following a high-fat meal if there is no difficulty in venepuncture

Equal amounts of the animal and vegetable fats used in our experiments produced approximately the same increase in coagulability

References overleaf

EFFECT OF PHYSICAL ACTIVITY ON INCREASED COAGULABILITY OF BLOOD AFTER INGESTION OF HIGH-FAT MEAL

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PREVIOUSLY we have adduced evidence which suggests that *one* factor which has a causal relationship to the increasing incidence of coronary atheroma and cardiac infarction may be the increase in dietary fat which has occurred over the past few decades (Fullerton et al 1953, Fullerton 1955, 1956) More recently we have shown that blood coagulability, measured by the recalcified plasma-clotting time (R P C), increases in approximately equal degree after the ingestion of animal fat (bacon, butter, and eggs) and vegetable fat (mainly margarine) (McDonald and Fullerton 1958) As Morris (1957) has pointed out, the increasing mortality from coronary-artery heart-disease has followed changes in vegetable-fat intake more closely than the alteration in animal-fat consumption, but he has stressed that epidemiological studies have failed to confirm the hypothesis of a single or simple dietary ætiology for ischæmic heart-disease We have already expressed a similar opinion (Fullerton 1956), and, in our view, attempts to explain the increasing incidence of coronary atheroma and cardiac infarction by reference to the single factor of greater fat consumption have confused the ætiological picture

Another trend which has been conspicuous in the past few decades has been the general decline of physical activity, largely owing to the increase in mechanisation of industry and in all forms of mechanical transport Morris et al (1953) advanced the hypothesis that men in physically active jobs have a lower incidence of coronary-artery heart-disease in middle age than men in physically inactive jobs, and pointed out that the disease is not so severe in physically active workers Further suggestive evidence has been provided by Brown et al (1957), who showed that among men in Birmingham aged 60-69 the prevalence of coronary-artery disease seemed to be unrelated to mental activity or smoking habits, but was fairly closely related to the physical demands of occupation, being highest for men in sedentary work Considerations such as these have prompted us to study the effect of physical activity on the increase in blood coagulability which follows ingestion of a high-fat meal

Methods

The experiments were carried out in healthy male medical students aged 20-27

" *Sedentary* " Day

On a weekday each student reported at the hospital at 8 30 A M, where, after a fasting venous-blood sample had been removed, he consumed a breakfast containing approximately 85 g fat ($2^1/_2$ oz bacon, 2 eggs, $1-1^1/_2$ oz butter, bread, and tea with milk and sugar) He reached hospital by private or public transport and the distance which had to be covered by walking did not exceed $^1/_2$ mile From 9 A M onwards he attended lectures and clinical instruction, walking approximately 200-300 yards in the intervals between them At 12 30 P M, $3^1/_2$ hours after completion of the breakfast, a second blood sample was obtained

TABLE I—R P C TIMES (SEC) FASTING (F) AND $3^1/_2$ HOURS AFTER 85 G FAT

Subject no	Sedentary			Active		
	F	$3^1/_2$ hr	Difference	F	$3^1/_2$ hr	Difference
1	136	135	1	137	130	7
2	151	108	43	129	121	8
3	140	109	31	133	121	12
4	129	116	13	138	124	14
5	125	121	4	132	126	6
6	123	107	16	143	136	7
7	161	137	24	126	123	3
8	158	140	18	121	110	11
9	133	92	41	108	105	3
10	154	104	50	139	115	24
11	158	123	35	134	130	4
12	152	118	34	146	138	8
13	137	116	21	132	132	0
14	135	121	14	136	135	1
15	147	124	23	143	135	8
16	122	110	12	133	133	0
Means	141 3	117 6	23 8	133 1	125 9	7 3

" *Active* " Day

On Saturday mornings the procedure adopted was exactly the same except that no classes were attended and each student observed the following schedule

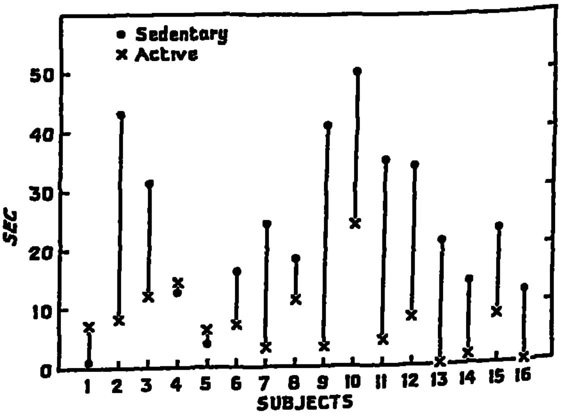
8 30-9 A M breakfast (fat content 85 g)
9-10 A M walking at a moderate pace for 3 miles
10-10 40 A M rest
10 40-11 40 A M walking for 3 miles
11 40-12 30 P M rest

Blood samples were again obtained before breakfast and $3^1/_2$ hours after it

In all cases coagulability was estimated by measuring the recalcified-plasma-clotting (R P C) time by the technique which we have described in a recent communication (McDonald and Fullerton, 1958) An alteration in the R P C time of 12 seconds or more has been regarded as significant

Results

23 subjects were observed on the " sedentary " day, and 16 of these on the " active " day as well The results in these 16 subjects are shown in table I and are represented diagrammatically in the accompanying figure 2 subjects (1 and 5), who showed no significant shortening of the R P C time at $3^1/_2$ hours while " sedentary ", are included in this group Because we were anxious to complete our observations before the start of a student vacation we later decided to observe, during the " active " day, only subjects who showed a significant reduction of



Reductions in R P C times $3^1/_2$ hours after 85 g fat

DR McDONALD, PROF FULLERTON REFERENCES

Biggs, R, Macfarlane, R G (1953) Human Blood Coagulation Oxford
Fullerton, H W, Davie, W J A, Anastasopoulos, G (1953) *Brit med J* ii, 250
— (1955) *Proc R Soc Med* 48, 664
— (1956) *Proc Nutr Soc* 15, 66
Keys, A, Buzina, R Grande, F, Anderson, J T (1957) *Circulation*, 15, 274
Macligan, N F, Billimoria, J D (1956) *Lancet*, ii, 235
O Brien, J R (1956) *ibid* ii, 232
— (1958) *ibid* i, 410
Pilkington, T R E (1957) *Clin Sci* 16, 261

TABLE II—R P C TIMES (SEC) FASTING (F) AND 3½ HOURS AFTER 85 G FAT

Subject	Sedentary		
	F	3½ hr	Difference
17	146	136	10
18	124	124	0
19	147	140	7
20	139	134	5
21	129	126	3
22	135	123	12
23	132	128	4
Means	136 0	130 1	5 9

R P C time at 3½ hours while "sedentary" The findings in the remaining 7 subjects are shown in table II

Table I and the figure show that in all the subjects except 2 (1 and 5), the R P C time at 3½ hours was significantly shorter (difference 12 seconds or more) than the fasting reading while the subjects were "sedentary", the mean reduction for all 16 subjects being 23 8 seconds The results obtained when the subjects undertook the moderate exertion described above were strikingly different The mean reduction for all 16 subjects at 3½ hours was only 7 3 seconds Omitting subjects 1 and 5, it is seen that the significant shortening (difference 12 seconds or more) at 3½ hours in the "sedentary" phase is abolished in eleven subjects (2, 6–9, 11–16) and is much less in 2 (subjects 3 and 10) as a result of the moderate exercise Subject 4 showed a barely significant reduction at 3½ hours, of the same degree during both the "sedentary" and "active" phases In no instance was the reduction of R P C at 3½ hours significantly greater on the "active" day than on the "sedentary" day

The results obtained in "sedentary" medical students have been significantly different from those found in convalescent ward patients, aged 20–61, with no history of cardiac disability (McDonald and Fullerton 1958) These are presented in table III, arranged in two age-groups—20–24 and 30+ It is seen that (1) the fasting R P C time in the convalescent-ward patients is significantly lower in both age-groups than in the students, (2) the reductions in R P C time in the convalescent patients are greater for both age-groups than in "sedentary" students, and (3) a significant reduction in R.P C time occurred at 3 and 4 hours in all 11 convalescent patients, whereas a significant shortening was found at 3½ hours in only 14 of 23 "sedentary" students It is proposed to extend these observations, but it seems probable that even the small amount of physical activity undertaken by the students on the "sedentary" days may be sufficient to account for the longer fasting R.P C time, and the less conspicuous shortening of this time 3½ hours after the intake of 85 g fat The activity undertaken by convalescent ward patients is, of course, very little and entails walking only a few yards

TABLE III—CONVALESCENT WARD PATIENTS R.P C TIMES (SEC) FASTING (F) AND 3 AND 4 HOURS AFTER 85 G FAT

Age (yr)	F	3 hr	Difference	4 hr	Difference
20	121	76	45	84	37
24	116	68	48	74	42
21	96	65	31	64	32
20	103	70	33	76	27
23	126	60	66	53	73
Means	112 4	67 8	44·6	70 2	42 2
33	122	74	48	98	24
36	111	76	35	85	26
49	105	75	30	76	29
50	114	86	28	82	32
58	132	99	33	96	36
61	109	80	29	77	32
Means	115 5	81 7	33 8	85 7	29 7

Discussion

The hypothesis that the incidence of coronary-artery disease is inversely related to the general level of physical activity accords well with the findings presented above If shortening of the R P C time can be regarded as indicating a greater tendency to fibrin formation in vivo, and if intravascular fibrin formation is the important factor leading to atheroma, it follows that any factor which operates over long periods and which can be shown to shorten the R P C time is likely to be causally related to the development of atheroma In our opinion two of these factors are high intake of fat and low level of physical activity It is clear that other factors are important in regard to the development of coronary atheroma, as is evident from consideration of the sex distribution and the constitutional predisposition to the development of this lesion, but these cannot be held to account for the increasing incidence In many respects coronary-artery heart-disease seems to be a penalty which must be paid for a "higher standard of living" Many changes are involved when this standard is raised, in addition to an increase in dietary fat and a decrease of physical activity, but, since these two changes have been shown to increase blood coagulability, it seems reasonable to regard them as more important than factors of which have not been assessed in this objective manner If the development of atheroma depends on a long-continued process which favours fibrin formation without a concomitant increase of fibrinolysis, and if physical activity operates in the way we have suggested, it follows that a high general level of activity may well be important in preventing the development of atheroma, whereas phases of much physical activity at long intervals in a sedentary life are unlikely to delay significantly the progress of atheroma The business executive who undertakes little physical activity throughout the week is unlikely to compensate for this by playing several rounds of golf at the weekend

One factor in addition to physical activity which varied between the three groups of subjects studied was the degree of mental activity This could be regarded as moderate in the "sedentary" students, and negligible in students on the "active" day and in the convalescent patients The reduction in R P C time after the high-fat breakfast was greatest in convalescent patients, intermediate in "sedentary" students, and least in physically active students In other words it was inversely proportional to physical activity but was not directly correlated with mental activity It may be that the mental activity of the students on the "sedentary" days was insufficient to produce a distinct effect on coagulability, and further studies under conditions involving different degrees and types of mental activity might be rewarding

Summary

The acceleration of the recalcified-plasma-clotting (R.P C) time after the ingestion of 85 g fat was, to a large extent, abolished by moderate physical activity

The fasting R P C time was shorter, and its reduction after 85 g fat was greater in convalescent-ward patients than in "sedentary" students

REFERENCES

Brown R G, Davidson L A G, McKeown, T, Whitfield, A G W (1957) *Lancet*, ii 1073
Fullerton H W, Davie, W J A, Anastasopoulos, G (1953) *Brit med J* ii 250
— (1955) *Proc R Soc Med* 48 664
— (1956) *Proc Nutr Soc* 15 66
McDonald G A Fullerton H W (1958) *Lancet*, ii 598
Morris J N, Heady J A, Raffle P A B, Roberts, C. G, Parks, J W (1953) *Lancet* ii, 1053
— (1957) *ibid* i, 410

NEPHROTIC SYNDROME AFTER THE APPLICATION OF MERCURY OINTMENT

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FOR many years mercurial salts have had the reputation of being dangerous to nervous and renal tissue In 1948 Warkany and Hubbard warned against the risk of pink disease when calomel is given for teething troubles they showed that children with this disease excrete large amounts of mercury in the urine Bivings and Lewis (1948) confirmed the relationship and reported good response to dimercaprol (BAL) in 1 case Pink disease, however, may not be the only risk Wilson et al (1952) reported 5 cases of renal disease, which may have been caused by calomel, and Farquhar (1953) described an infant who developed pink disease at five months and fatal kidney damage a year later More recently Stoneman (1958) reported pink disease in siblings following the application of ung hydrarg ammon to the anal margins

Case-report

A lorry-driver, aged 52, was admitted to hospital in June, 1957, complaining of swelling of his ankles for a fortnight He had also noticed some breathlessness on effort and mild, gnawing, upper-abdominal pain after meals for a few weeks For over ten years he had suffered intermittently from psoriasis and he had been advised to rub in an ointment containing 5% ammoniated mercury, 15% tar, and 2% salicylic acid He had done this very regularly

On examination he had puffy eyelids and ankle œdema There was a psoriatic rash on his chest and limbs His urine contained albumin, 4 g per 100 ml There was no other abnormality his blood-pressure was 140/90 mm Hg. The serum-cholesterol was 650 mg per 100 ml, plasma-proteins 3 7 g per 100 ml (albumin, 1 3 g, globulin, 2 4 g), and blood-urea 26 mg per 100 ml The serum electrolytes, liver-function tests, chest X-ray, and barium meal were normal

The diagnosis of nephrotic syndrome was made and the patient was started on a high protein low-salt diet He was also given repeated double-strength plasma transfusions, acetazolamide, and katonium ion-exchange resin Despite this, his condition became worse his œdema rose to his thighs and sacrum, and he developed a small area of consolidation in one lung In view of this deterioration the diagnosis of mercurial poisoning was considered and the urinary excretion of mercury estimated This was 240 μg in twenty-four hours The patient was then started on a therapeutic trial of dimercaprol and the mercury excretion-test was repeated The twenty-four hour excretion was 640 μg on the fourth day of treatment and 1241 μg on the ninth day By the eighteenth day it had fallen to 84 μg From then onwards improvement was maintained Five months later the patient was completely well and the blood and urine findings were normal For safety's sake he was given a second course of dimercaprol

Conclusion

A patient developed a nephrotic-type illness following the application during many years of an ointment which contained ammoniated mercury, tar, and salicylate The high urinary excretion of mercury and the immediate clinical response to treatment with dimercaprol suggests that the cause of the illness was mercury poisoning The nervous system was not involved, and the renal changes were reversible

Because of the wide use of mercury salts the possibility of this complication is worth remembering

Our thanks are due to Dr R R Hughes, under whose care the patient was treated, and who made the diagnosis We should also like to thank Dr H G Farquhar for his help and Dr Hugh McLean, Dr Eve Patterson, and Mr R L Grainger for the laboratory estimations

REFERENCES

Bivings, L, Lewis, G (1948) *J Pediat* 32, 63
Farquhar, H G (1953) *Lancet*, ii, 1186
Stoneman, M E R (1958) *ibid* i, 938
Warkany, J, Hubbard, D M (1948) *ibid* i, 829
Wilson, V K, Thomson, M L, Holzel, A (1952) *Brit med J* i, 358

TREATMENT OF INTERMITTENT CLAUDICATION WITH VITAMIN E

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OPINION on the value of vitamin E in the treatment of peripheral vascular disease differs widely

Boyd et al (1949) reported favourably on its use in a series of 81 patients with intermittent claudication Boyd classifies these patients into three types type I are those in whom, on continuing walking or exercise, the pain disappears, type II are those in whom the pain attains a certain level and eventually the patient stops because of persistence of pain, and type III are those who stop because of its increasing severity He stated that all type-I cases obtained good results with vitamin E, in type II, 27 out of 72 obtained good results, 32 were improved, and 13 were unrelieved, whereas in type III the therapy had *no effect* This report, however, is open to criticism as the series did not appear to be adequately controlled

Baer and Heine (1949) threw doubt on the efficacy of the vitamin, and Hamilton and Wilson (1952) also reported unfavourable results, but in a very small series of cases Hamilton et al (1953) later reported a controlled series of 41 cases and expressed the opinion that vitamin E was of no value in the treatment of intermittent claudication This report has been criticised on the ground that the patients were treated for only twelve weeks

This discrepancy between different reports encouraged us to carry out a controlled experiment in a series of patients with intermittent claudication

Material

The series consisted of 40 non-diabetic male patients with obliterative vascular disease who complained of intermittent claudication *Males were selected for the ease of obtaining* adequate numbers, as well as to eliminate any possible sex difference in response

In all cases symptoms had been present *for at least* five years, and in all cases the pain was felt in the calf muscles 3 patients had had lumbar sympathectomy without lasting improvement All had received physiotherapy, and some had had grafts without lasting improvement

The average age of the control group was 57, and that of the vitamin-E group 55 9 There were 3 patients aged 40–50 in each group

Following Boyd's grading we found we had no cases of type I The distribution of the patients is shown in table I

Discussion

Any trial such as this is beset by many difficulties and possible sources of error Although we adopted the Boyd grading, in order to make some sort of classification, it seemed to us open to considerable criticism owing to the different reactions of patients to pain The time taken for pain to pass off varied widely in successive records, and this time was of little value in assessing our final results For example, several of the patients with poor exercise tolerance recovered remarkably quickly, and it can only be assumed that these patients anticipated the onset of pain and stopped before it became severe There was little difference between the ages of patients in the two groups, and each group included 3 cases of the younger age-groups

The average increase of 15 circuits in the group receiving vitamin E, compared with 2 5 in the control group, represents a considerable difference, which contrasts with the very slight increase noted by Hamilton et al (1953) These patients, of course, would show a much greater improvement when walking on level ground

As would be expected, cases of proximal thrombosis with a good collateral circulation benefited more than cases with extensive obliterative changes—although 2 cases of proximal thrombosis were included in our failures There was no significant improvement in the nutrition of the skin in any case

Six months after the end of the trial, of the treated patients who had improved none had deteriorated, and 3 patients in the control group who had been transferred to vitamin E at the end of the trial reported some improvement

Conclusion

Many criticisms can be applied to this study, but certain simple facts seem to emerge 13 of a final series of 17 patients on vitamin E improved, where as only 2 of a control group of 17 showed improvement In successful cases the patients are now carrying on their work with ease, and enjoying their leisure Apparently vitamin-E therapy does confer benefit in some cases

All these patients had undergone certain forms of therapy before undergoing this test, and had been disappointed with the results The fact that improvement was observed in most patients only after some months makes it unlikely that psychological factors played a part

It is well known that intermittent claudication will sometimes improve without any sort of treatment (Hamilton and Wilson 1952), but in our patients this explanation is unlikely because of the duration of their symptoms

We were unable to form any criteria which would enable us to select cases which would respond to vitamin-E therapy We confirmed Boyd's observations that large doses are necessary, and that treatment must be continued for a considerable period We also found that there is considerable delay before any response can be noted, and we concluded that therapy should be continued for at least three months before being abandoned

We owe a debt of gratitude to Roche Products for their help and cooperation throughout the trial, and particularly to Dr Margaret Briggs, their medical director

REFERENCES

A M , Ratcliffe, A H , Jepson, R P , James, C W H (1949) *J Bone Surg* 31B, 325

G A , Heine W I (1949) *J Amer med Ass* 139, 733

on, M , Wilson G M (1952) *Quart J Med* 21, 169

— — Armitage, P , Boyd, J T (1953) *Lancet*, i, 367

CORTISONE AS COVER FOR MAJOR SURGERY IN ADVANCED PULMONARY TUBERCULOSIS

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PATIENTS who had collapsed with peripheral circulatory failure after major operations for advanced pulmonary tuberculosis were observed by me to improve remarkably after administration of cortisone (Edge 1956) There were no untoward effects on the residual tuberculous disease, and I suggested that such patients were suffering from adrenocortical deficiency

The present paper describes 17 patients with advanced pulmonary tuberculosis for whom major surgery was considered to offer the only real hope of permanently arresting the disease Each was a very poor surgical risk owing to the bad general condition, and the twenty-four-hour urinary 17-ketosteroid output before operation was found to be low in each case Replacement steroid therapy was given before, during, and after operation, in order to anticipate possible operative or postoperative collapse.

Clinical Material

There were 17 patients (14 male, 3 female), whose ages ranged from 26 to 58 (mean 45) The operations carried out were pneumonectomy in 5, lobectomy in 4, local excision of cavity in 1, and thoracoplasty in 7 The patients have been followed up for from six to twenty-one months after operation.

Extent of Disease

Chest radiography showed the number of zones involved to range from 3 to 6 (mean 5 1), the total cavity diameter ranged from 4 to 12 cm (mean 6 8 cm)

Sputum Status

The sputum of all 17 patients on admission to hospital contained tubercle bacilli on smear, and 12 remained sputum-positive up to the time of operation The remaining 5 became sputum-negative between two and four months before operation A significant level of bacterial resistance was demonstrated in 10 patients, in 3 the organisms were shown to be fully sensitive, whilst in 4 no information is available

Urinary Excretion of 17-Ketosteroids

Twenty-four-hour urinary excretion of 17-ketosteroids was measured by the modified Callow-Zimmerman technique (Dyke 1951) In the 3 women excretion ranged from 1 5 to 4 2 mg per twenty-four hours (mean 3 2 mg) (mean normal value in females, 9 mg per twenty-four hours), and in the 14 men from 2 8 to 8 9 mg per twenty-four hours (mean 6 7 mg) (mean normal value in males, 15 mg)

The twenty-four-hour 17-ketosteroid excretion was also measured in 10 men (aged 24–58, mean 41) all of whom had pulmonary tuberculosis of more limited extent, which was responding satisfactorily to antibacterial treatment alone, and all of whom were in very good general condition In these patients the values were higher than in those with advanced disease, ranging from 8 8 to 18 0 mg daily (mean 13 0 mg) These figures correspond with those cited by Dyke (9–23 mg [mean 15 mg] per twenty-four hours) as normal for males

Replacement Cortisone

When the resting urinary twenty-four-hour 17-ketosteroid excretion was found to be low, cortisone by mouth was started three days before operation in a daily dosage of 100 mg (25 mg six-hourly), this was continued for a week after operation, and then reduced in weekly steps of 25 mg to 75, 50, and 25 mg daily The total duration of treatment was four weeks

Postoperative Course

Mortality

There were three postoperative deaths 1 patient died a week after operation from uræmia due to renal amyloid disease, the 2nd died suddenly, on the third day after pneumonectomy, from spontaneous pneumothorax on the good side, and the 3rd, who carried organisms highly resistant to streptomycin, isoniazid, and *p*-aminosalicylic acid, died of bronchopleural fistula ten weeks after operation

Complications

The remaining 14 had no postoperative complications, apart from transient basal collapse in 1 instance The postoperative course was remarkably free of incident, the patients remained free of fever, dyspnœa, hypotension, and tachycardia and on the day after operation looked and felt none the worse for the operation The pink colour and lack of any suggestion of dehydration were particularly striking Wound healing proceeded quite normally in all cases

Late Results

2 patients have a persistent cavity with consistently positive sputum at nine and twelve months after thoracoplasty, 1 showing total and one partial bacterial resistance 2 patients remained culture-positive for three and six months after thoracoplasty, but have been since negative up to fifteen and twenty months respectively The other 10 patients, followed for from six to twenty-one months after operation, have remained radiographically and clinically satisfactory with consistently negative sputum on smear and culture

Discussion

Steroid hormones have been shown to be of value in the preparation and management of patients undergoing major surgery, apparently acting in one of three ways (1) by replacing a known deficiency of endogenous steroids in conditions such as Addison's disease and pituitary failure (Troen and Rynearson 1956), (2) by correcting a presumed adrenocortical deficiency in malignant and other wasting diseases (Ruddell and McKeown 1956, Szilagyi et al 1952, Cole et al 1953), or (3) by suppressing the disease process in conditions such as ulcerative colitis and hæmolytic anæmia, thus affording an opportunity for surgical treatment (Abbott et al 1955)

It has been shown by Forbes et al (1947) that patients with various chronic debilitating diseases (though not including tuberculosis) commonly have a low excretion of 17-ketosteroids in the urine, these patients do not respond to medical or surgical insults by an increase in steroid output, as do normal people (Sandberg et al 1954) In corollary, several workers have pointed out the greatly increased risk of surgery in patients whose adrenal function had been suppressed by steroid therapy, and in whom replacement had not been continued over the operative period (Hayes 1956, Allanby 1957, Slaney and Brooke 1957), while Popert and Davis (1958) found no increased liability to postoperative complications in a group of patients whose long-term steroid treatment was continued over the operative period

Earlier fears of activating any tuberculous infection present appear to be ill founded, provided adequate antibacterial treatment is also given (Houghton 1954) In the present series the giving of cortisone for four weeks to 10 patients with resistant organisms was followed by bronchopleural fistula in only 1 instance, thus might have been expected in any case in view of the high level of resistance present

With the increasing use of long-term chemotherapy, major surgery for pulmonary tuberculosis is being increasingly reserved for patients with far-advanced disease in whom chemotherapy alone is inadequate Many such patients present a formidable, and sometimes prohibitive, surgical risk

The operative mortality (18%) in the present series was certainly no higher than might have been expected bearing in mind the nature of the clinical material, in each case death was directly due to a definitive complication unrelated to stress The equanimity with which the remaining patients tolerated the stress of operation was remarkable

The present study suggests that it would be useful further to investigate adrenal function in patients debilitated by tuberculosis or other chronic illness who require major surgery, with a view to replacing adrenal steroids where these are found to be deficient

Summary

17 patients with far-advanced pulmonary tuberculosis, in very poor general condition, were submitted to major surgery Each had a low twenty-four-hour urinary 17-ketosteroid excretion before operation, and the operative period was covered by oral administration of cortisone

There were 3 postoperative deaths from definitive complications unrelated to stress The remaining patients tolerated operation well It is suggested that the replacement of deficient endogenous adrenal secretion contributed substantially to their recovery

My thanks are due to Mr J S Glennie and Mr P Jewsbury, who operated on the patients, and to Dr J E Horrocks and his staff who carried out the urinary 17-ketosteroid estimations The expenses of this work were defrayed by a grant from the Research subcommittee of the Manchester Regional Hospital Board.

REFERENCES

Abbott, W E., Kreiger, H., Levey, S (1955) *Ann intern Med* 43, 702
Allanby, K D (1957) *Lancet*, i, 1104
Cole, W H., Grove, W J, Montgomery, M M (1953) *Ann Surg* 137, 718
Dyke, S C (1951) Recent Advances in Clinical Pathology, p 222 London
Edge, J R. (1956) *Tubercle*, 37, 166
Forbes, A P, Donaldson, E. C., Reifenstein, E C, Albright, F (1947) *J clin Endocrin* 7, 264
Hayes, M A (1956) *Surgery*, 40, 945
Houghton, L E (1954) *Lancet*, i, 595
Popert, A J, Davis, P S (1958) *ibid* i, 21
Ruddell, J S, McKeown, K. C. (1956) *Med Times*, 84 255
Sandberg, A A, Eik-Nes, K., Samuels, L T, Tyler, F H. (1954) *J clin Invest* 33, 1509
Slaney, G, Brooke, B N (1957) *Lancet*, i, 1167
Szilagyi, D E., Marguild, R. R., Jay, G D (1952) *Arch Surg* 65, 21
Troen, P, Rynearson, E H. (1956) *Clin Endocrin Metab* 16, 747

" the scholar is in duty bound to remain unconvinced except upon the most solid assurances, and no one is a whit the worse for his indecision Now compare his situation with ours, where sick, frightened folk look to us eagerly for treatment, advice, and reassurance The scholarly fellow who says 'It may be so and so, but the evidence is incomplete', has little to offer to the sick in body and mind We are here in a domain more pristine than that of reason, a territory where symbols possess immense power. Some of us in our modern wisdoms run a danger of losing touch with the fears of our patients We sneer at their dependence on the bottle of medicine, and say they must be weaned from their fanciful attachment In situations—and they are frequent—in which we are relatively helpless, the bottle of medicine is often the most potent and most economical psychotherapy There are signs that some patients are being weaned from the bottle—to what? In place of the simple bottle we have to substitute the hypodermic syringe, the psychotherapist, the X-ray apparatus, the physiotherapy department "—Dr R E HOPE SIMPSON, *J Coll gen Practrs*, August, 1958, p 225

URINARY δ-AMINOLÆVULIC ACID AND PORPHOBILINOGEN IN DIFFERENT TYPES OF PORPHYRIA

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During attacks of acute intermittent porphyria (A I P) increased amounts of porphobilinogen are regularly excreted in the urine Waldenstrom (1937) found that in families with A I P several siblings excreted porphobilinogen in the urine without showing symptoms of porphyria Such cases were regarded as latent A few persons who had had attacks of typical acute porphyria did not excrete porphobilinogen in their urine when investigated by the methods then available The question thus arose whether the presence of some earlier porphyrin-precursor in the urine might not be a more reliable criterion of the porphyria-carrier trait

Recently Mauzerall and Granick (1956) devised a more sensitive method for quantitative determination of porphobilinogen than that described by Vahlquist (1939) They found that the precursor of porphobilinogen, δ-aminolævulic acid, was also present in large amounts in the urine of 2 patients with acute porphyria, and they devised a method for quantitative determination of this substance Small amounts of δ-aminolævulic acid (ALA) as well as porphobilinogen (PBG) were found even in normal urine

Material and Methods

Quantitative determinations by the method of Mauzerall and Granick (1956) were made of δ-aminolævulic acid and porphobilinogen in urine from 50 healthy adults, 50 healthy children (aged from seven months to fourteen years), 34 patients with A I P, and 128 of their closest relatives, as well as from 12 patients with porphyria cutanea tarda It was not always possible to obtain twenty-four-hour samples therefore the results are given in mg per 100 ml

At first determinations of the uro- and copro-porphyrins were made semiquantitatively by the method used by Waldenström (1937) Spectral analyses were made of the acid extracts in a Baly cuvette The following scale was used

Thickness of layer—>20 mm = negative 20–15 mm =(+) 15–8 mm =+ 8–1 mm =++—<1 mm =+++

Later the uroporphyrin was determined quantitatively according to Askevold (1951) and calculated according to Rimington and Sveinsson (1950) with corrected factor according to With (1955) As early as 1939 Waldenström and Vahlquist emphasised, however, that quantitative determination of uroporphyrin in acute porphyria is of little value, since porphobilinogen is readily converted to uroporphyrin

Coproporphyrin was determined by Askevold's modification (1951) of Fischer's original method, with the exception that the last washing was done with a fresh aqueous 1/200 dilution of a 1% solution of iodide in alcohol according to Schwartz, Zieve, and Watson (1951) with calculation according to Rimington and Sveinsson (1950) and corrected factor according to With (1955)

Results

Normal Values

The values of urinary δ-aminolævulic acid and porphobilinogen in 50 healthy adults and 50 healthy children are given in table I

To exclude errors due to varying concentrations of urine, in the latter part of the investigation the urinary excretion of δ-aminolævulic acid and porphobilinogen was calculated in relation to the excretion of creatinine Table II shows the normal values when calculated in this way

TABLE I—NORMAL URINARY CONTENT OF δ-AMINOLÆVULIC ACID AND PORPHOBILINOGEN

	δ-aminolævulic acid (mg per 100 ml)		Porphobilinogen (mg per 100 ml)	
Adults	M–0 305	S D–0 133	M–0 105	S D–0 046
Children below 15 years	M–0 257	S D–0 115	M–0 047	S D–0 031

TABLE II—NORMAL URINARY CONTENT OF δ-AMINOLÆVULIC ACID AND PORPHOBILINOGEN

	δ-aminolævulic acid (mg per g creatinine)		Porphobilinogen (mg per g creatinine)	
Adults	M–1 9	S D–0 6	M–0 7	S D–0 4
Children below 15 years	M–3 7	S D–1 4	M–0 6	S D–0 3

Normal urinary content of uroporphyrin
Semiquantitative method negative
Quantitative method 0–15 µg per l (25 healthy adults)

Normal urinary content of coproporphyrin
Semiquantitative method (+)
Quantitative method 0–175 µg per l (50 healthy adults)

Patients with Acute Intermittent Porphyria and their Relatives

The results of the analyses in the different groups are shown in table III and figs 1–3

Of 45 persons in group 3, 10 (22%) had latent porphyria The siblings examined were from 23 different families with 37 known cases of manifest A I P This brings the frequency of latent and manifest porphyria up to

TABLE III—ACUTE INTERMITTENT PORPHYRIA

Group	No of cases	Normal excretion of ALA and PBG	Pathological excretion of ALA and PBG	Pathological excretion of ALA only	Pathological excretion of PBG only
1 Acute manifest intermittent porphyria	34	0	29	0	5
2 Offsprings of patients with latent or manifest porphyria					
<15 years	31	21	1	0	9
>15 years	24	18	1	0	5
3 Siblings of patients with latent or manifest porphyria	45	35	7	0	3
4 Nephews and nieces of patients with latent or manifest porphyria					
<15 years	12	12	0	0	0
>15 years	9	9	0	0	0
5 Apparently healthy parents (but genetically certain carriers of the porphyria trait) of patients with latent or manifest porphyria	7	0	6	0	1
Total	162	95	44	0	23

ALA = δ aminolævulic acid PBG = porphobilinogen

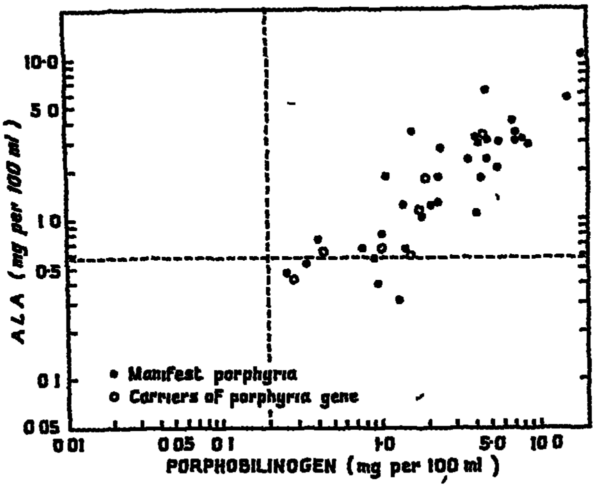

Fig 1—ALA and porphobilinogen urinary excretion of 34 patients with manifest porphyria and of 7 genetically certain carriers of the porphyria trait The line parallel to the ordinate corresponds to M+2S D mg porphobilinogen per 100 ml, the line parallel to the abscissa to M+2S D mg ALA per 100 ml Logarithmic scale

57% The value must be somewhat too high, but it does support the widely accepted assumption (Waldenstrom 1937, 1956 and others) that the trait of A I P is inherited as a simple dominant factor

If a person's child and one of his parents, or a brother or sister, or a nephew or niece had latent or manifest A I P, he was said to be a genetically certain carrier of the porphyria trait Urine was obtained from 7 subjects satisfying these criteria These carriers, who had never had symptoms of A I P, were between thirty-seven and seventy-one years In 6 the excretion of δ-aminolævulic acid as well as of porphobilinogen was increased, in the 7th the porphobilinogen only was raised Thus the values were pathologically increased in all of them (fig 1) This shows that latent porphyria can remain latent even in the older age-groups It also suggests that the disease can be transmitted only by persons with latent or manifest A I P This assumption is strengthened by the observations made in group 4, where neither the δ-aminolævulic acid nor the porphobilinogen levels were increased in the urines of offsprings of healthy siblings of patients with A I P

Patients with Porphyria Cutanea Tarda

According to Waldenstrom (1957) this heterogenous group can be divided into at least two subgroups—porphyria cutanea tarda symptomatica, and porphyria cutanea tarda hereditaria or protocoproporphyria The classification of most cases is difficult and must be regarded as tentative until further facts are known It has since been recommended by Rimington (1958)

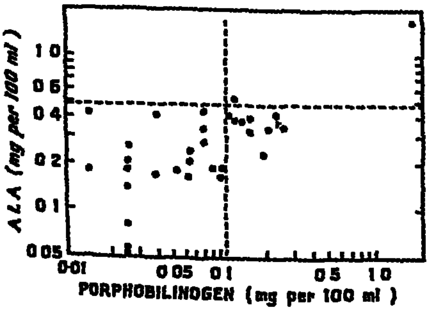

Fig 2—ALA and porphobilinogen urinary excretion of 31 offspring, below 15 years, of patients with latent or manifest porphyria The line parallel to the ordinate corresponds to M+2S D mg porphobilinogen per 100 ml, the line parallel to the abscissa to M+2S D mg ALA per 100 ml (both for children below 15 years) Logarithmic scale

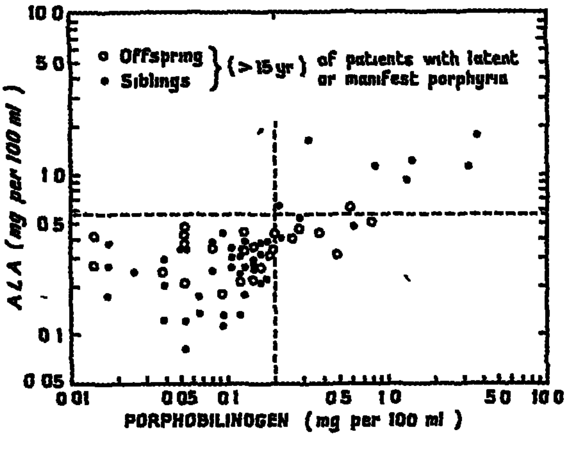

Fig 3—ALA and porphobilinogen urinary excretion of 24 offspring and 45 siblings of patients with latent or manifest porphyria The line parallel to the ordinate corresponds to M+2S D mg porphobilinogen per 100 ml, the line parallel to the abscissa to M+2S D mg ALA per 100 ml Logarithmic scale

Porphyria cutanea tarda symptomatica —This type is mainly characterised by cutaneous symptoms It usually appears in middle age and has a chronic, benign course It is often accompanied by liver dysfunction The excretion of porphobilinogen is usually normal

Protocoproporphyria —This type usually becomes manifest around puberty Here the cutaneous symptoms may be accompanied by colicky pain and rarely by neurological signs During

TABLE IV—PORPHYRIA CUTANEA TARDA

Case no	Sex	Age at onset in years	Urine analyses			
			δ-amino-lævulic acid (mg per 100 ml)	Porpho-bilinogen (mg per 100 ml)	Uro-porphyrin (µg per l)	Copro-porphyrin (µg per l)
			1 Porphyria cutanea tarda symptomatica			
1	F	16	1 401 0 996 0 287 0 291	0 052 0 090 0 102 0 179	+++ +++ + 11	+ + neg 108
2	F	72	0 085 0 268	0 102 0 192	+++ 2674	++ 231
3	M	35	0 221	0 025	++	(+)
4*	M	42	0 442	0 124	3145	466
5*	M	54	0 320	0 124	1360	483
6	M	76	0 136 0 301 0 089	0 014 0 102 0 063	+++ 938 1903	+ 378 228
			2 Protocoproporphyria			
7	F	10 mos	0 348	0 140	7272	895
8	F	2	0 230	0 124	4040	250
9	F	?	1 217	0 337	++	
10	F	9	0 202	0 124	++	+
11	F	55	0 282 0 056 0 315	0 124 0 025 0 167	2457 2069 1868	544 482 322
12	M	45	0 611 0 296 0 268	0 077 0 154 0 124	++ 875 252	Neg. 105 68

Bold faced figures exceed M + 2 S.D for the age-group and are therefore considered pathological
* Alcoholic

attacks of colic the porphobilinogen is often increased Large amounts of proto- and copro-porphyrins are present in the fæces even during remissions During attacks the fæces are said to contain less porphyrins and the urine more This reciprocity in the excretory function of liver and kidneys was first noted by Rimington (1952) The large family in South Africa reported by Dean (1953, 1955) certainly represents this type of porphyria

The results of the analyses in cases of porphyria cutanea tarda are shown in table IV

Urine samples from some of the closest relatives of patients 11 and 12 were also analysed A sixteen-year-old son of case 12 showed a slightly increased excretion of δ-aminolævulic acid and porphobilinogen on two occasions without simultaneous increase in the excretion of porphyrins Two older brothers of case 11, on the other hand, showed a normal excretion of δ-aminolævulic acid and porphobilinogen, while the excretion of porphyrins was increased in both The proband (case 11) in this family was a fairly heavy drinker, and it is possible that alcohol, by its toxic effect on the liver, unmasked her latent porphyria It seems quite probable that a genetical defect (a real porphyria) must be present when an alcoholic develops porphyria cutanea tarda

Summary

Quantitative determinations were made of δ-aminolævulic acid and porphobilinogen in the urine from 34 patients with manifest acute intermittent porphyria, from 128 of their closest relatives, and from 12 patients with porphyria cutanea tarda

All patients with latent or manifest acute intermittent porphyria showed a pathologically increased excretion of porphobilinogen in the urine This therefore appears to be an obligatory diagnostic sign In two-thirds of the patients the excretion of δ-aminolævulic acid was also increased

In all apparently healthy but genetically certain carriers of the disease the urinary excretion of porphobilinogen, and usually of δ-aminolævulic acid as well, was increased This suggests that the disease can be transmitted only by persons with latent or manifest porphyria

A third of the apparently healthy children, below 15 years, of patients with latent or manifest acute intermittent porphyria had biochemical disorders suggestive of porphyria It is noteworthy that so many of these children had latent porphyria, since manifest porphyria is very rare in this age-group

In patients with porphyria cutanea tarda the urinary excretion of δ-aminolævulic acid and of porphobilinogen followed no regular pattern Determination of the porphyrin content of the urine and fæces thus appears more useful in the biochemical diagnosis of this type of porphyria

The investigation was supported by grants from the Medical Faculty of the University of Lund

I wish to thank Prof A Querido of Leiden, Holland, and Dr G Dean of Port Elizabeth, South Africa, for contributing urine samples from patients 7, 8, and 9

REFERENCES

Askevold, R (1951) *Scand J clin lab Invest* 3, 318
Brunsting, L A (1954) *Arch Derm Syph* 70, 551
Dean, G (1953) *Brit med J* ii, 1291
— Barnes, H D (1955) *ibid* ii, 89
Mauzerall, D, Granick, S (1956) *J biol Chem* 219, 435
Rimington, C, Sveinsson, S L (1950) *Scand J clin Lab Invest* 2, 209
— (1952) *Acta med scand* 143, 161
— (1958) *Brit med J* i, 640
Schwartz, S, Zieve, L., Watson, C J (1951) *J Lab clin Med* 37, 843
Vahlquist, B (1939) *Hoppe-Seyl Z* 259, 213
Waldenström, J (1937) *Acta med scand* suppl 82
— Vahlquist, B (1939) *Hoppe Seyl Z* 260, 189
— (1956) *Acta genet* 6, 122
— (1957) *Amer J Med* 22, 758
With, T K (1955) *Scand J clin Lab Invest* 7, 193

POSTOPERATIVE INFECTION IN UROLOGY

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URINARY infection has long been accepted as the commonest complication of operation on the prostate and bladder, and in fact is often regarded as a necessary evil Infection mostly produces only local inflammation with no serious consequences, and eventually, if all goes well, it dies out some months after the patient has left hospital. Occasionally it may lead to serious and sometimes fatal results by way of secondary hæmorrhage, pyelonephritis, and septicæmia It is therefore obvious that, if these occasional serious consequences are to be avoided, great efforts must be made to maintain sterility of the urine after all urological operations

In the work described here, which has occupied three years, we have had two main objects to investigate the origin and clinical effects of postoperative infection of the urinary tract and blood-stream, and to find means of preventing infection

Methods

Except for some of the patients in whom the clinical effects of infection are described, only those whose urine was sterile before operation are included in this report Of 161 such patients 41 had retropubic prostatectomy and 120 had transurethral operations on the prostate or the bladder They were admitted to four general surgical wards under the care of two surgeons whose technique did not change significantly throughout the investigation Antibiotics and sulphonamides were not given before operation and were only used when the clinical condition of the patient was thought to make them necessary after operation Preoperative drainage was not used, and at operation a plastic or a latex-rubber catheter was placed in the urethra and left in for three days At first open drainage was used A sterile rubber tube connected to the catheter hung over the edge of the bed and drained into a pail on the floor When clots caused obstruction they were either washed out with sterile saline solution or removed by suction from a sterile bladder syringe Later, closed drainage and irrigation were used, as described below

Urine was collected with aseptic precautions by one of us each day, starting on the day before operation and omitting Sundays During the later part of the investigation the following material for culture was taken from patients while in the theatre swabs from the anterior urethra before instrumentation, urine collected when the cystoscope was passed, fragments of prostate removed by resection, and samples of the irrigating fluid After operation, specimens were collected either by disconnecting the catheter from the drainage tube or, when patients were on closed irrigation, with a sterile syringe attached to a needle inserted into the wall of the tube, previously swabbed with tincture of iodine Preliminary tests showed that neither procedure caused contamination of the specimens Urine was examined within two hours of collection by microscopy of wet and gram-stained smears of deposit and by a roughly quantitative cultural technique Six standard loopfuls ($^1/_{150}$ ml) of uncentrifuged urine were placed side by side on well-dried blood-agar and MacConkey plates One loopful was streaked over the remaining surface of each plate, which was then incubated as soon as the other loopfuls had soaked into the medium Colonies were counted and identified after twenty-four hours

The sensitivity of all the bacteria to antibiotics and the biochemical activities of the gram-negative bacilli were determined by standard methods Most strains of *Staphylococcus aureus* were phage-typed (Williams and Rippon 1952)

A patient was considered to have developed an infection only if his urine contained at least 3000 bacteria per ml. on two or more consecutive days This high limit was chosen to eliminate slight or doubtful infections When an organism appeared first in small numbers and later became numerous, the infection was counted as starting on the day of its first appearance. Infections by coagulase-negative staphylococci (*Staph albus*) were not included, because the clinical significance of this organism was often doubtful. It was often found in the urethra and, in small numbers, in otherwise normal urine Though its presence in larger numbers was in some cases accompanied by pyuria, in others there was no evidence of inflammation.

Results

Bacteriology of Urine

Between April 4, 1955, and July 25, 1956, before additional measures were taken to prevent infection. 13 of the 16 retropubic prostatectomies and 29 of the 41 transurethral operations were followed by infection, an overall incidence of 74% The incidence of infection was much higher than was indicated by the clinical signs and symptoms and higher than would have been detected if only one or two random postoperative samples of urine had been examined from each patient, because some infections cleared in a few days The bacteria, in order of frequency, were coliform bacilli proteus, *Staph albus*, *Streptococcus fæcalis*, *Staph aureus*, and *Pseudomonas pyocyanea*, but in many cases the infections were mixed. As we reported previously (Gillespie 1956), many of the bacteria originated in the hospital, as was shown by their abnormal resistance to antibiotics and, in the case of staphylococci, by their phage patterns That cross-infection is often responsible for postoperative urinary infection has been shown by several workers (Ørskov 1952, 1954, Kass 1955, Goldie 1956, Dutton and Ralston 1957) The organisms do not usually come from the patient's own bowel. Gillespie (1956) and Dutton and Ralston (1957) failed to isolate antibiotic-resistant coliform bacilli from the fæces of patients in whom they caused urinary infection.

All the patients with infections had numerous pus cells in their urine, but bacteria often appeared a day or two before the pus Pus cells were rarely numerous in the absence of infection.

Clinical Effects

Pyrexia higher than 100°F on one or more days of the postoperative period was recorded in 48% of 155 patients chosen at random Of the patients who remained without postoperative infection, and whose records showed such pyrexia, 82% were affected in this way only on the first or the second postoperative day Considering, therefore, records of pyrexia from the third day onwards, we found that only 5 of 79 (6%) of patients who remained uninfected showed pyrexia, whereas 42 of 76 (55%) of patients with infection had pyrexia which was probably attributable to the infection

The duration of the infection varied from a few days to more than a year Many patients were followed up, but it was impossible to see all at regular intervals About a third of those who left hospital with an infection had sterile urine after three months, and about two-thirds after six months A few were still infected a year later It seems that infection usually clears up spontaneously when the operation site heals and treatment with sulphonamides or antibiotics is often unnecessary. If used, these drugs usually do not influence the ultimate disappearance of the organisms, whose persistence for a long period often indicates a structural abnormality of the urinary tract.

In a few patients infection had serious consequences, with the development of pyelonephritis In others, not included in this series, we have, during the past two years, seen 1 proved case of subacute bacterial endocarditis and 9 of septicæmia complicating postoperative urinary infection In 5 cases, 2 of which were fatal, the septicæmia was a complication of an established pyelonephritis and caused deterioration in the condition of an already ill patient. In the 4 others, the picture was more dramatic, with sudden collapse of a previously fit patient owing to a profound fall in blood-pressure but combined with a rise of temperature, 1 of these patients died, and the 3 others recovered after prompt energetic treatment with intravenous antibiotics This condition of bacteriæmic shock is an important complication of urological infection and urethral instrumentation (Waisbren 1951, Hall and Gold 1955, Spittel et al 1956 Ezzo and Knight 1957) It may easily be mistaken for massive pulmonary embolism or severe coronary thrombosis if the strange combination of shock and pyrexia is not noticed, and the result is often fatal unless intravenous antibiotics are quickly given Even at necropsy the real cause of death may not be obvious

There is often a rise of temperature, and occasionally a rigor, soon after withdrawal of the indwelling catheter, and it seems likely that the disturbance of an infected operation site may sometimes discharge bacteria into the blood-stream To investigate this possibility, three blood-cultures were made from each of 51 patients of whom 29 had sterile urine and 22 infected urine at the time of operation The first sample of blood for culture was taken immediately before withdrawing the catheter the second within five minutes of its removal, and the third about twenty minutes later

All blood-cultures were negative from 15 patients whose urine remained sterile after operation but of 14 patients who developed postoperative urinary infection 7 had positive blood-cultures from blood taken within five minutes of withdrawing the catheter, whereas their first and third samples of blood were negative. The results with the patients who came to operation with urine already infected suggested that bacteriæmia was less likely with long-standing infection than with recently acquired infection. In 15 of this group whose urinary flora was unchanged after operation no positive blood-cultures resulted from withdrawing the catheters, but of 7 whose urine after operation contained new varieties of bacteria 2 had positive blood-cultures from blood obtained within five minutes of withdrawal (table I) Organisms

TABLE I—BLOOD-CULTURES TAKEN FIVE MINUTES AFTER REMOVING THE INDWELLING CATHETER FROM PATIENTS WITH STERILE AND INFECTED URINE

Urine before operation	Urine when catheter removed	No of patients	Blood-cultures	
			Positive	Negative
Sterile	Sterile	15	0	15
	Infected	14	7	7
Infected	No additional organisms	15	0	15
	Additional organisms acquired	7	2	5
	Total	51	9	42

similar to those causing bacteriæmia were present in the urine of 6 of the patients (Slade 1958)

Evidently, transient bacteriæmia commonly follows the withdrawal of an indwelling catheter from a recently infected urinary tract, and the difference between this bacteriæmia and a septicæmia may be a matter of the number and virulence of the organisms These results recall those of Scott (1929) and Barrington and Wright (1930), who showed that transient bacteriæmia sometimes results from the passage of sounds used to dilate urethral strictures Bacteriæmia was also found by these workers when urine was passed for the first time after dilatation

Sources and Routes of Infection

Culture of prostatic fragments often yielded a few colonies of *Staph albus* but no other organism Bacteria similar to those which caused infection were sometimes isolated from the anterior urethra just before operation but not from numerous swabs of theatre personnel, towels, cystoscopes and other equipment, and sterilising and rinsing solutions On the other hand, it was always easy to find the organisms on ward equipment and furniture Irrigation of the bladder in the ward has been shown to be an important cause of infection, and improvements in drainage and irrigation methods can reduce its incidence (Pyrah et al 1955, Gillespie 1956, Goldie 1956) Dutton and Ralston (1957) showed experimentally that bacteria could ascend to the bladder via the drainage tube and indwelling catheter, and we have found that rising air-bubbles can readily carry organisms up the tube But bacteria must also enter the bladder in other ways, for some patients developed infection even when treated with closed aseptic drainage and no irrigation (Gillespie 1956) We therefore decided to investigate the effects of improving methods of bladder drainage and irrigation and of changing methods of sterilising urethral instruments in the theatre

PREVENTION OF INFECTION

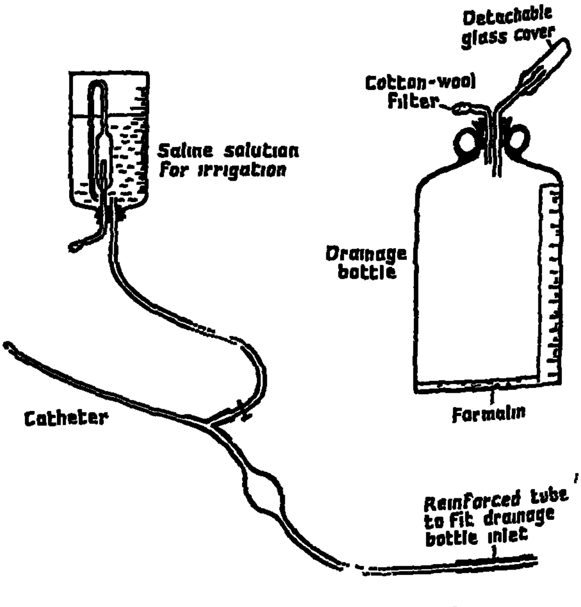
Closed Drainage

The closed-drainage system was set up before the patients left the theatre, by aseptically connecting the indwelling catheter to the sterilised drainage apparatus by means of a 4-ft length of sterile rubber tubing The apparatus was prepared beforehand by inserting a rubber stopper fitted with glass inlet and air filter, previously autoclaved, into a 1 gallon 2-handled clear glass bottle (U G B Co , A L 29), containing 100 ml of liq formaldehyde *B P C* The assembled unit was allowed to stand for at least twenty-four hours before use, because tests showed that cultures of *Escherichia coli*, proteus, *Ps pyocyanea*, and *Staph aureus*, smeared on the inside of the bottle above the level of the fluid, were killed by exposure overnight to the vapour In order to allow the contents to be measured for fluid-balance records, volume scales were printed on paper strips which were fixed to the outsides of the bottles (see figure)

In a controlled trial previously reported (Gillespie 1956) we found that the onset of infection was often delayed, but usually not prevented, by the closed aseptic drainage system Our experience subsequently has been similar As compared with patients on open drainage, many could be brought through the two or three days of catheter drainage after operation without infection, only to develop an infection soon after the catheter was removed

Closed Irrigation

An entirely closed method of irrigation was introduced, so that patients whose catheters became blocked by blood-clot after operation could be irrigated with complete aseptic precautions A 1-litre bottle of sterile saline solution was suspended 1 metre above the bed The air inlet was fitted with a sterile cotton-wool filter kept dry by means of a non-return fitting The delivery tube of the saline bottle was connected to a glass Y-piece by means of a rubber tube fitted with a screw clip The stem of the Y-piece was connected to the indwelling catheter and the other limb to one end of a Higginson syringe from which both valves had been removed The other end of the syringe was connected to the closed drainage bottle (see figure) The bladder was washed out by allowing saline solution to flow up the catheter by gravity If clots prevented this, the saline solution was made to flow into the Higginson syringe until it had displaced all air-bubbles there The supply was then stopped with a screw clip and, pinching the lower tube of the syringe with finger and thumb, the contents of the syringe were forced up the catheter by compressing the bulb with the other hand When suction was needed to move clots from the catheter, the catheter was pinched by finger and thumb and the bulb emptied into the drainage bottle by compression with the other hand The lower tube of the syringe was then pinched just beyond the bulb and the catheter released, thus allowing the bulb to expand and producing enough suction to remove all but very big clots from the bladder These manipulations, although complicated to


Detachable glass cover
Cotton-wool Filter
Saline solution for irrigation
Drainage bottle
Catheter
Formalin
Reinforced tube to fit drainage bottle inlet

Apparatus for closed drainage and irrigation

ABLE II—INFECTIONS IN RELATION TO METHOD OF WASHING OUT BLADDER

Method	No of patients	Infected within 18 hr after operation	"At risk for infection later	Infection developed during		Total infected
				Remainder of catheter drainage	Subsequently	
Closed irrigation	25	11	14	3	3	17
No irrigation	19	4	15	0	4	8
Total	44	15	29	3	7	25
Open irrigation	19	5	14	8	1	14

describe, proved easy to demonstrate to the nursing staff, who soon learned to perform them correctly Occasionally, however, this closed method of irrigation failed when bleeding was profuse and clotting pronounced, and the tubing had to be disconnected to allow the use of a sterile bladder syringe With increasing practice these failures have been limited recently to those cases where neither closed nor bladder-syringe irrigation proved successful, and the catheter had to be changed Such difficulties, with their consequent risk of infection, could normally be avoided by careful observation of the patient during the early hours after operation Obstruction to the passage of urine was easy to relieve if dealt with promptly

The effect of using closed irrigation was tested between Aug 1, 1956, and Nov 11, 1957 Some patients, selected at random, had the closed-irrigation apparatus fitted in the theatre The others also had closed drainage but had wash-outs of sterile saline solution from a sterile syringe when clots had to be removed. The result was a disappointingly small improvement Infection developed in 25 (57%) of the 44 patients who either had closed irrigation or required no irrigation, compared with 14 (74%) of the 19 with open irrigation It was seen that the incidence of infection in the immediate postoperative period (up to eighteen hours after operation) was quite unaffected (table II) The reduction in the incidence of infection in the remaining period of catheter drainage was, however, highly significant. On open irrigation, 8 of the 14 patients then "at risk" developed infection before the catheter was removed, whereas with closed or no irrigation, only 3 of 29 patients similarly "at risk" developed infection during drainage (χ^2, corrected for continuity, = 8·5, n = 1, p less than 0·01) Those who had no irrigation of any sort appeared to do best, but the number of patients was too small to be sure of this Patients who required no irrigation may have been less susceptible to infection Patients who survived without infection until the catheter was withdrawn often developed persistent infections within twenty-four hours after the withdrawal The organisms causing these delayed infections did not differ from the others It seemed that bacteria might persist in the operation site, only to be released and sometimes to cause infection after the disturbance of withdrawing the catheter If so, the infections which developed after the removal of the catheter, like the immediate postoperative infections, might be attributable to bacteria introduced in the theatre and would reduce the benefit obtained from aseptic drainage and irrigation of the bladder That this may happen was shown by culturing material adhering to the collapsed bulb of Foley catheters Of 16 catheters removed from patients whose urine was sterile, 4 yielded heavy growths of bacteria other than *Staph albus* Similar organisms were isolated from their urine soon afterwards, but had disappeared by next day and did not cause urinary infection in these particular patients

Changes in Theatre Technique

A study of our records showed that several patients had developed early postoperative infections by organisms similar to those known to be present in the urine of previous patients on the same operating-list (Many patients came to operation with urine already infected following previous instrumentation or operation in this or other hospitals) In 1 instance, the infecting organism was *Staph aureus* phage-type 77, which had not recently been isolated from the patient's own ward where an investigation of staphylococci was in progress, but was present in the urine of an earlier patient on the same list who came from a different ward It seemed clear from these findings, and from the constantly high incidence (about 30%) of early postoperative infection despite improved drainage and irrigation that some infections must originate in the theatre by cross-infection within an operating-list Although swabs taken from time to time from urethral instruments had been sterile, incomplete sterilisation of the instruments was the most likely cause of the cross-infection

Two changes were therefore introduced patients with urinary infections were kept, as far as possible, to the end of the operating-list (an obvious precaution which previously had been overlooked), and the method of disinfecting cystoscopes and resectoscopes was altered Boilable cystoscopes were not available The instruments in use had previously been disinfected between cases by dismantling, rinsing in running water, and immersing for at least fifteen minutes in 1/2000 mercuric oxycyanide solution contained in shallow dishes Hayes (1949) showed that oxycyanide was a poor disinfectant—a fact which we have confirmed Immersion for thirty minutes failed to sterilise strips of metal contaminated with *Staph aureus*, and proteus and coliform bacilli survived for twenty minutes Chlorhexidine ('Hibitane') was found to be a much better disinfectant and sterilised large inocula of the same organisms within ten minutes, using a 1/5000 solution in saline A mixture of hibitane and oxycyanide had a slightly more rapid bactericidal action than hibitane alone Further studies are being made on the bactericidal action of this mixture (Media containing sodium thioglycollate, lecithin, and 'Lubrol' were used for bactericidal tests with the disinfectants) Accordingly, we decided to employ an aqueous solution containing 1/5000 hibitane and 1/2000 mercuric oxycyanide for disinfecting cystoscopes and resectoscopes between operations The instruments were taken apart, washed in running water, and immersed vertically, so

TABLE III—INCIDENCE OF INFECTION WITH "OLD" AND "NEW" ASEPTIC METHODS IN THEATRE (SEE TEXT FOR EXPLANATION)

—	Total patients	Infections				
		Within 18 hr after operation	In remaining catheter-drainage period	In next 24 hr	Subsequently	Total
'Old' method (Aug 1, 1956 to Nov 10, 1957)	44	15	3	4	3	25
'New' method (Nov 11 1957 to March 8, 1958)	30	2	2	3	0	7

All patients had closed or no irrigation and closed drainage.

as to expel air, in tall cylinders containing the disinfectant mixture, for at least twenty minutes These changes were introduced on Nov 11, 1957 Of the 30 patients who had operations after this date only 7 (23%) developed infection, compared with 25 (57%) of the 44 previous patients who also had closed irrigation and drainage (table III) The difference was significant ($\chi^2 = 6\ 8$, n = 1, p less than 0 01) Much of the improvement was due to a striking reduction in the incidence of early postoperative infection

In contrast to the antibiotic-resistant "hospital organisms" which caused many of the infections before Nov 11, those responsible for all 7 subsequent infections were normally sensitive to antibiotics and may have been derived from the patients themselves Urethral swabs showed that organisms similar to those which caused 4 of the infections (a coliform bacillus, a streptococcus, and, on 2 occasions, *Ps pyocyanea*) were present in the anterior urethra before operation, and these may have been carried up by instrumentation

Since the changes in ward and theatre technique were introduced, there has been a gradual reduction in the infection-rate The incidence of postoperative infection has fallen from 74% of the 57 patients treated by the old methods, before August, 1956, to 23% of the 30 patients treated since Nov 11, 1957 The difference is highly significant (χ^2, corrected for continuity = 18 3, n = 1, p less than 0 001) Both types of operation have shared in the improvement, only 2 of the 10 recent retropubic operations and 5 of the 20 recent transurethral operations have been followed by infection

Discussion

Urinary infection is a very common complication of operation on the prostate and bladder, and is usually the result of cross-infection with antibiotic-resistant organisms derived from the hospital and brought about by instrumentation Its true incidence may be unsuspected since it often produces little clinical disturbance Nevertheless it is important to prevent infection, because of its serious results in a minority of patients It sometimes leads to pyelonephritis, which is probably a blood-borne infection resulting from the transient bacteriæmia that we have detected in many of these patients, and this must be particularly dangerous to a patient with impaired renal function Bacteria are most likely to enter the bloodstream during the first few days of an infection while the operation site is still unhealed Their entry may be precipitated by the removal of the indwelling catheter or perhaps by straining at defæcation or micturition The important complications of bacteriæmic shock, septicæmia, and bacterial endocarditis seem likely to be further extensions of this process

The changes in our methods of preserving asepsis during and after operation have considerably reduced our infection-rate and have given us the new and welcome experience of performing urological operations and carrying treatment through to its conclusion in a sterile surgical field The results of culturing preoperative urethral swabs suggest that some infections were caused by bacteria which entered the urethra before operation McLeod (1958) has demonstrated the importance of this mode of infection Another possible route of infection is through the secretion which collects between the urethral wall and the indwelling catheter Although we were previously unable to demonstrate the entry of infecting organisms by this route (Gillespie 1956) the experiments of Kass and Schneiderman (1957) show that it may be important

Summary

Urological patients with initially sterile urine were studied in general surgical wards for a period of three years

Postoperative urinary infection was very common, and was usually caused by antibiotic-resistant bacteria endemic in the hospital Several patients with infected urine suffered transient bacteriæmia when their indwelling catheters were removed It is suggested that such bacteriæmia may sometimes lead to pyelonephritis, septicæmia, bacteriæmic shock, or endocarditis

The infection originated sometimes in the theatre and sometimes in the ward Considerable improvement was achieved by changing the method of disinfecting cystoscopes and resectoscopes and by using of closed aseptic apparatus for draining and irrigating the bladder after operation

We wish to thank the board of governors of the United Bristol Hospitals for a grant towards the cost of this research, and the ward sisters and Mr W Price for their enthusiastic assistance

REFERENCES

Barrington, F J F, Wright H D (1930) *J Path Bact* 33, 871
Dutton, A A C, Ralston, M (1957) *Lancet*, i, 115
Ezzo, J A, Knight, W A, Jr (1957) *Arch intern Med* 99, 701
Gillespie, W A (1956) *Proc R Soc Med* 49, 1045
Goldie, W (1956) *ibid*, p 1047
Hall, W H, Gold, D (1955) *Arch intern Med* 96, 403
Hayes, W (1949) *Brit J Urol* 21, 198
Kass, E H (1955) *Amer J Med* 18, 764
— Schneiderman, L J (1957) *New Engl J Med* 256, 556
McLeod, J W (1958) *Lancet*, i, 394
Ørskov, I (1952) *Acta path microbiol scand* suppl 93, 259
— (1954) *ibid* 35, 194
Pyrah, L N, Goldie, W, Parsons, F M, Raper, F P (1955) *Lancet*, ii, 314
Scott, W W (1929) *J Urol* 21, 527
Slade, N (1958) *Proc R Soc Med* 51, 331
Spittel, J A, Martin, W J, Nichols, D R (1956) *Ann intern Med* 44, 302
Waisbren, B A (1951) *Arch intern Med* 88, 467
Williams, R E O, Rippon, J E (1952) *J Hyg, Camb* 50, 320

THE INFLUENCE OF AGE ON EXCRETION OF RADIOACTIVE IODINE

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MEASUREMENT of the urinary excretion of radioactive iodine (^{131}I) has proved valuable in the diagnosis of hyperthyroidism We suspected, however, that this test was not as reliable in the elderly as it was in younger patients To see whether the limits of normality varied with age, a group of euthyroid patients of different ages were reviewed

Material and Methods

In the ^{131}I-excretion test used at this hospital, urine is collected during three periods in the forty-eight hours following the administration of the iodine The percentage of the dose excreted during the 0–8-hour period, the 8–24-hour period, and the 24–48-hour period is measured, and a thyroid-uptake or "T" index is calculated from the formula $T = \frac{(0\text{–}8)\ \text{hours}\ \% \times 100}{(8\text{–}24)\ \text{hours}\ \% \times (0\text{–}48)\ \text{hours}\ \%}$ This procedure gives results relatively independent of renal function The currently accepted normal range of the T-index is 2 8 – 13 (Fraser et al 1953)

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In 1952-57 the test was performed on more than 2000 patients 203 cases (with ages ranging from 20 to 82) were selected from this group To ensure, as far as possible, that these cases were euthyroid, the following criteria were used No patients known to have thyroid or renal disease, or in whom the T-index was greater than 13, were included All cases referred with a provisional diagnosis of hyperthyroidism or myxoedema were likewise excluded, even though the result of the test was within the normal range The reasons for performing the test in the cases chosen for analysis are shown in table I

10 of the 213 tests made on these cases were excluded because errors in urine collection were suspected † The remaining 203 results from 197 patients (147 female and 50 male) were analysed by plotting the T-index, and the excretion values for the individual urine-collection periods against the patient's age

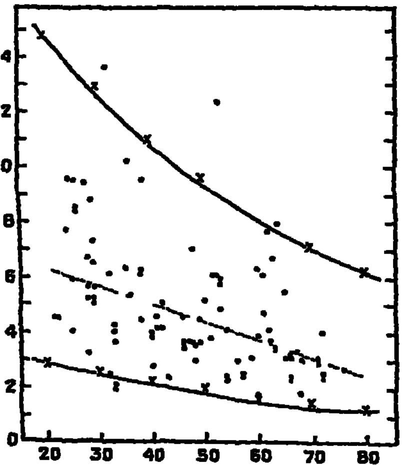

Fig 1—T-index plotted against age The equation for the regression (broken) line is T=7·55 −0·065 age (years) The upper and lower solid lines contain 95% of the points.

Results

In fig 1 it will be seen that the value of the T-index decreases with advancing age This is shown by the calculated regression line, which has a slope of −0·065 T-units per year of age ($P<0·001$) The correlation coefficient of the T-index with age is −0·42±0·07 The distribution of the points suggests that the relationship between the T-index and age may be curvilinear rather than linear A significant decline is also obtained when log T is plotted against age, and the log T-age regression line was used in calculating the limits of normality shown in fig 1 95% of the values lie within these limits

TABLE I—COMPOSITION OF THE GROUP OF PATIENTS WHOSE TESTS WERE COMPARED

Reason for test	Age 20–49		Age 50–82		All ages	
	Tests	Mean T-index	Tests	Mean T-index	Tests	Mean T-index
Before thyroid ablation with ¹³¹I for heart disease	23	4·8	25	4·8		
Before hypophysectomy for cancer	3	4·5	22	3·0		
To exclude hyperthyroidism in clinically euthyroid patients with (a) neurosis	31	5·4	3	4·6		
(b) no apparent disease	38	6·5	38	3·6		
Miscellaneous e g, menstrual disorders	16	4·9	4	4·0		
Total	111	5·6	92	3·8	203	4·8
Selected euthyroid group	47	5·7	19	4·2	66	5·1

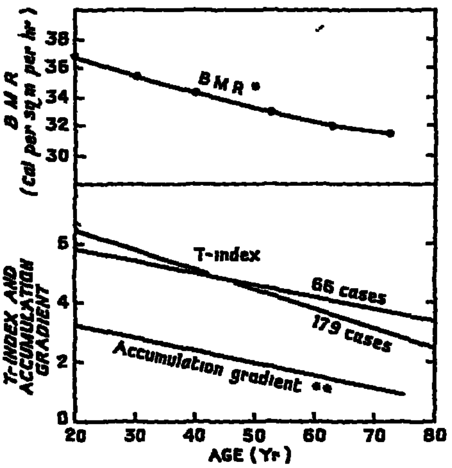

Fig 2—Comparison of the slopes of the regression lines for the T-index and accumulation gradient The fall in the basal metabolic rate is also shown (*from Robertson and Reid 1952, **from Perlmutter and Riggs 1949)

This decline in the T-index might be due to lack of uniformity in the composition of the group Comparison of the diagnoses of the cases above and below 50 years of age shows that there are proportionately more patients with cancer in the older age-group and more cases of neurosis in the younger (table I) However, the decrease is observed even when these cases are discarded Moreover, analysis of the results obtained in an additional group of 66 subjects selected from hospital personnel and outpatients showed a similar decline in the T-index with advancing age In this smaller group, chosen as controls because they were clinically euthyroid, the age range was 20–73 years, the slope of the regression line was −0·042 ($P<0·02$), and the correlation coefficient of the T-index with age was −0·28 ($P<0·02$)

The correlation between age and the percentage of ¹³¹I excreted during the separate collection periods is shown in table II Excretion in the first 8-hour period falls with increasing age The percentage excreted in the 8–24-hour period increases with age, as does that for the entire 48-hour period The fall in the 0–8-hour value could be due to impairment of renal function through ageing The increase in the 8–24-hour and 0–48-hour excretion cannot, however, be explained in this way It is more likely that the increased excretion and the change in the T-index are due to a fall in thyroid uptake

TABLE II—CORRELATION BETWEEN ¹³¹I-EXCRETION AND AGE IN 197 PATIENTS

Urine sample	Correlation coefficient r	Significance P
0–8-hour period	−0·222	<0·01
8–24-hour period	+0·332	<0·001
0–48-hour period	+0·368	<0·001
T-index	−0·420	<0·001

Discussion

A decrease in thyroid uptake with advancing age has been reported in previous ¹³¹I studies Perlmutter and Riggs (1949) found that in a group of 162 euthyroid cases the mean "accumulation gradient", derived from the 1–4-hour neck uptake, fell with each decade from the age of 12 to over 70 Quimby et al (1950), in a survey of 1050 tests on euthyroid patients, also detected a smaller but statistically significant decrease in the 24-hour thyroid uptake with increasing age The rate of decline of the accumulation gradient with age observed by Perlmutter and Riggs (1949) closely resembles that of the T-index in our series Calculated from their data, the slope of the regression line is −0 048 units per year The fall in the thyroid uptake with advancing age in euthyroid patients revealed by these tests also runs parallel to the decrease in the basal metabolic rate (Robertson and Reid 1952) (fig 2) An age-correction factor, such as is used for the basal metabolic rate, would therefore probably increase the sensitivity of the ^{131}I-excretion test Our data suggest that in patients over 50, results in the " upper normal " range (T-index 9–13) may indicate hyperthyroidism

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† In every test the T-index was compared with the 0–48-hour excretion value The results were outside the range found in 95% of cases, in the 10 rejected tests

Summary

^{131}I-excretion tests in a series of euthyroid patients were analysed The results showed that the uptake of ^{131}I by the thyroid gland decreases with advancing age

We gratefully acknowledge advice and assistance from Prof Russell Fraser, and assistance in the statistical analysis from Mr N W Please

REFERENCES

Fraser, R , Hobson, Q J G , Arnott, D G , Emery, E W (1953) *Quart J Med* 22, 99
Perlmutter, M , Riggs, D S (1949) *J clin Endocrin* 16, 724
Quimby, E H , Werner, S C , Schmidt, C (1950) *Proc Soc exp Biol , N Y* 75, 537
Robertson, J D , Reid, D D (1952) *Lancet*, i, 940

THE EFFECT OF INSULIN-BINDING ANTIBODIES ON INSULIN SENSITIVITY

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By the use of ^{131}I-labelled insulin, two abnormalities of insulin metabolism have been demonstrated in the sera of patients previously treated with insulin (*a*) binding to serum-globulins (Berson et al 1956), and (*b*) delayed disappearance from the circulation (Berson et al 1956, Welsh et al 1956) It has been suggested that repeated administration of insulin results in the formation of specific antibodies which migrate electrophoretically as globulins, injected insulin then becomes attached to the circulating antibody and is retained in the plasma instead of undergoing its normal course of degradation (presumably by tissue insulinase (Berson et al 1956) Furthermore, since insulin must be in contact with cells to exert its biological action, it has been postulated that binding to antibody would prevent such contact and result in apparent insulin unresponsiveness (Welsh et al 1956)

Various studies have clearly shown that patients with gross insulin resistance do have serum-globulin components which are probably antibodies, and which have an insulin-neutralising effect when injected with insulin into mice (De Fillipis and Iannocone 1952, Sehon et al 1955, Colwell and Weiger 1956) But it is still uncertain whether the " ordinary " diabetic patient acquires a significant degree of resistance to insulin as the result of antibodies developing

We have attempted to test the hypothesis concerning the effects of insulin antibodies and to determine the clinical significance of such antibodies

Methods

The patients studied had maturity-onset diabetes (recognised after age 35), but no other recognisable metabolic disturbance Fourteen had been treated with insulin for 6 months or longer, while eleven had not received insulin therapeutically

Insulin responsiveness in the patients was determined by a procedure based on measurement of blood-glucose half-life (Heller, Kalant, and Hoffman) A glucose load was administered intravenously over 5 minutes, and 20 minutes was allowed for its equilibration in body fluids During this interval a glucose infusion was given at a rate sufficient to maintain a raised blood-sugar concentration Over the next 30 minutes samples of capillary blood were obtained every 5 minutes, and from these the rate of fall of blood-sugar and its half-life ($t_{\frac{1}{2}}$G) were calculated Insulin[1] (0 1 u per kg) was then injected intravenously and sampling was continued for the next 30 minutes to permit calculation of blood-sugar half-life after insulin ($t_{\frac{1}{2}}$I)

In rabbits insulin responsiveness was assessed after the intravenous injection of crystalline insulin, 0 2 u per kg , by measuring the blood-glucose concentration every 10 minutes for 90 minutes and determining, in arbitrary units, the area between the time-curve of glucose concentration and the base-line drawn at the level of the initial concentration The dose of insulin was found by preliminary experiment not to produce a maximum hypoglycæmic effect in normal rabbits

Paper electrophoresis of serum containing labelled insulin was performed using 50 µl of serum applied in a line 3 inches toward the cathode from the middle of the strip, and allowed to move to the middle by hydrodynamic flow (Berson et al 1956) before electrophoretic separation The strips were dried and stained, and divided into eight sections albumin, α_1, α , β, and γ globulins, a band extending 1 cm on either side of the line of application (origin), the band between γ-globulin and origin, and a blank taken from the area on the anodal side of the albumin Eight strips were run simultaneously for each sample of serum and the appropriate segments pooled for assay of radioactivity in a scintillation well counter

Boundary electrophoresis was carried out in a Perkin-Elmer apparatus, model 38A, with barbitone buffer, pH 8 6, ionic strength 0 1 Aliquots of the serum were removed after resolution, by means of a needle-tipped pipette, by observation of the Schlieren pattern on the ground-glass screen it was possible to remove, from the descending limb, aliquots containing γ, $\gamma+\beta$, and $\gamma+\beta+\alpha_2$ globulin, and from the ascending limb those of albumin $+\alpha_1$ globulin, and of albumin $+\alpha_1+\alpha$ globulin Each aliquot was measured for total protein, by biuret reaction or nitrogen determination, and for radioactivity A concentration diagram of serum components was drawn from the Schlieren pattern and the relative composition of each aliquot removed from the electrophoresis cell was calculated (fig 1)

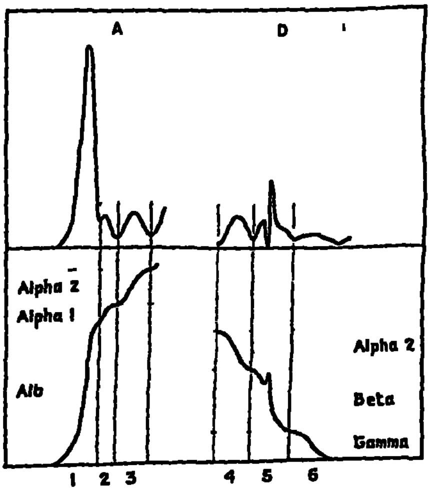

Fig 1—Method of calculating specific activities of serum-proteins after separation by moving-boundary electrophoresis

Above Schlieren pattern Below Concentration diagram of serum components calculated from the Schlieren pattern Specific activities of albumin and , -globulin were calculated directly, their contribution of radioactivity to segments 2 and 5 were calculated, and specific activities of α_1 and β then obtained by difference A ascending limb D descending limb

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[1] Insulin labelled with ^{131}I was obtained commercially, it had a specific activity varying from 3 to 6 mc per mg

By reference to the total protein measurements it was then possible to calculate the actual composition of each aliquot

The specific activities were measured directly for the first aliquot removed from each limb (γ-globulin from the descending and albumin-α_1 from the ascending) From the composition of the second aliquots ($\gamma+\beta$ from the descending, albumin $+\alpha_1+\alpha_2$ from the ascending) the contribution of γ and albumin-α_1 to the radioactivity of these fractions was calculated, and by difference the specific activity of β and α_2 were obtained In some cases albumin was obtained separately from α_1-globulin, the specific activity of the latter was then calculated from the second ascending aliquot, and that of α_2 was taken as the mean value obtained from the third aliquots of each limb

To study the rate of removal of insulin from plasma, a known amount of insulin-^{131}I was injected intravenously, the serum radioactivity precipitable by 10% trichloroacetic acid was measured 15 minutes later and expressed as percentage of injected dose present in the circulating plasma volume (as calculated from surface area and hematocrit) (Welsh et al 1956) In the experiments on patients this procedure was used simultaneously with measurement of insulin responsiveness, the total dose of injected insulin (labelled + carrier) being that necessary for the latter purpose In the rabbit experiments the two parameters were measured on different days The choice of the 15-minute interval minimised the relative importance of radiation-damaged insulin, which apparently has a longer half-life in serum than does native insulin (Berson et al 1956)

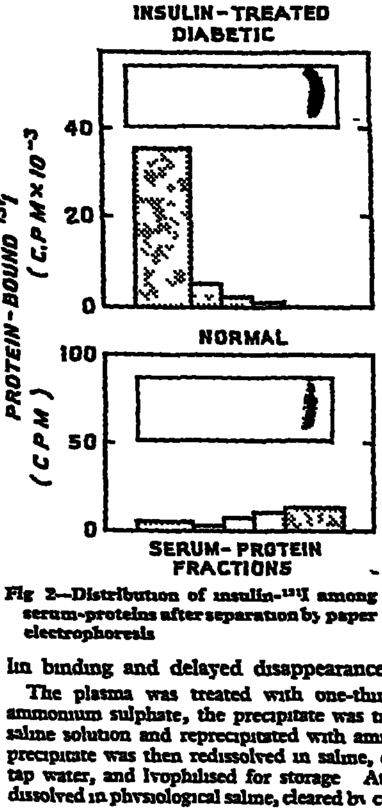

Fig 2—Distribution of insulin-^{131}I among serum-proteins after separation by paper electrophoresis

Rabbits were actively immunised against beef insulin[2] by the method of Arquilla and Stavitsky (1956) Passive immunisation was performed with plasma-proteins obtained from diabetic patients who demonstrated the phenomena of globulin binding and delayed disappearance of ^{131}I-insulin.

The plasma was treated with one-third volume of saturated ammonium sulphate, the precipitate was taken up in physiological saline solution and reprecipitated with ammonium sulphate The precipitate was then redissolved in saline, dialysed against running tap water, and lyophilised for storage At the time of use it was dissolved in physiological saline, cleared by centrifugation and infused into the femoral vein The amount of protein in the infusions varied from 0·5 to 1·0 g in 85–100 ml

Insulin-neutralising activity of serum was assessed in groups of five mice previously fasted for 6 hours

The glucose concentration of tail blood was measured before and 45 minutes after the intraperitoneal injection of insulin (2 or 6 milliunits in 0·01 ml) mixed with 0·2 ml of serum, the fall in glucose concentration was compared with that produced by the same amounts of insulin injected with 0·2 ml saline Blood-sugar was measured by Somogyi's (1952) modification of the Nelson method

Results

Insulin Responsiveness in Diabetic Patients

In agreement with the results of Berson et al (1956) it was found that the insulin-treated diabetic patients retained labelled insulin in their circulation longer than the untreated diabetic patients, and on paper electrophoresis most of it was found to be associated with γ-globulin On electrophoresis of serum from untreated patients most of the radioactivity remained at the origin, and the remainder showed no preferential association with a particular protein component (fig 2)

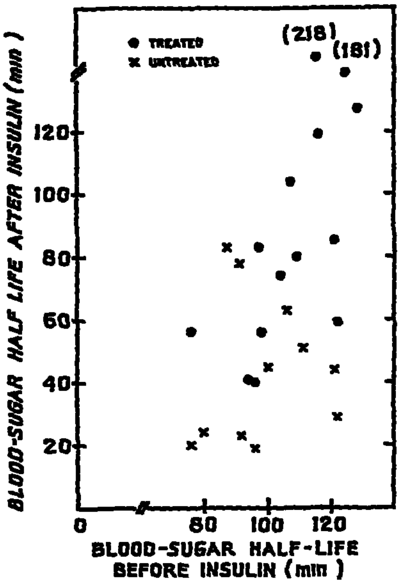

Fig 3—Relation between half-life of blood-sugar before insulin and that after insulin (0·1 u per kg) in treated and untreated diabetic patients

It has been previously shown for diabetics that, as the half-life of blood-glucose without insulin ($t_{\frac{1}{2}}G$) increases, there is a concomitant increase in the half-life after an injection of insulin ($t_{\frac{1}{2}}I$) (Heller, Kalant, and Hoffman) Consequently, to facilitate comparison of the insulin response of two groups, subjects having the same range of values of $t_{\frac{1}{2}}G$ were chosen When they were thus selected, the untreated diabetic patients were found to have lower values for $t_{\frac{1}{2}}I$ (44±7 minutes) than the treated diabetic patients (94±14 minutes), indicating a greater fall in $t_{\frac{1}{2}}$ in response to insulin ($P<0·01$) in untreated diabetics (fig 3 and table I)

The response to insulin may be defined as ($t_{\frac{1}{2}}G-t_{\frac{1}{2}}I$), since in non-diabetic subjects $t_{\frac{1}{2}}I=20±6$ minutes

TABLE I—INSULIN RESPONSE, SERUM RETENTION, AND GLOBULIN-BINDING OF INSULIN IN TREATED AND UNTREATED DIABETIC PATIENTS

Patient	$t_{\frac{1}{2}}G$	$t_{\frac{1}{2}}I$	$\frac{t_{\frac{1}{2}}G-t_{\frac{1}{2}}I}{t_{\frac{1}{2}}G-20}$	Insulin in plasma at 15 min. (% of dose)	Insulin bound to globulin (% of plasma-insulin at 15 min)
A-1	100	45	·69	11	5
A-2	111	51	·66	17	3
A-3	75	26	·89	16	5
A-4	76	20	1·00	17	0
A-5	92	23	·96	20	7
A-6	61	20	1·00	15	2
A-7	96	19	1·01	14	6
A-8	106	63	·50	14	3
A-9	122	29	·91	13	7
A-10	80	24	·93		
A-11	87	83	·06		
A-12	121	44	·76		
A-13	91	78	·18		
B-1	161	116	·32	35	54
B-2	121	85	·36	13	2
B-3	209	90	·63	25	33
B-4	274	168	·42	18	14
B-5	126	130	−·04	23	43
B-6	181	130	·32	63	37
B-7	98	56	·54	72	48
B-8	116	119	·03	81	62
B-9	97	83	·18	72	66
B-10	107	104	−·03		
B-11	76	56	·36		
B-12	128	127	·01		
B-13	94	41	·72		
B-14	96	40	·74		
B-15	115	218	−1·08		
B-16	124	181	−·55		
B-17	109	80	·33		
B-18	104	74	·36		
B-19	122	59	·62		

A = not treated with insulin.
B = treated with insulin.

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[2] Zinc insulin crystals were kindly supplied by Dr W R Kirtley of Eli Lilly and Co Indianapolis Ind and by Dr R G Romans, Connaught Laboratories, University of Toronto

(Heller, Kalant, and Hoffman), the normal insulin response may be taken as (t_1G–20) The relative response in diabetic patients can then be calculated as the ratio $\frac{t_1G - t_1I}{t_1G - 20}$ There was no significant degree of correlation between the insulin response so calculated, on the one hand, and the serum retention of insulin or binding of insulin to serum-globulin on the other (table II) There was a positive correlation between the latter two parameters

Active Immunisation of Rabbits to Insulin

Six normal adult rabbits were immunised against crystalline beef insulin Before and after this process, four parameters of insulin metabolism were studied (1) insulin responsiveness, (2) the globulin-binding of insulin-^{131}I, (3) the rate of disappearance from the circulation of injected insulin-^{131}I, and (4) the presence of circulating insulin-neutralising activity In addition, the sera of the immunised rabbits was tested [3] for insulin antibodies by the method of Arquilla and Stavitsky (1956) The results (table III) indicate that immunisation led to the development of hæmagglutinating antibodies to insulin, a decrease in the rate of disappearance of insulin from the circulation, and globulin-binding There was a direct relation between the amount of insulin remaining in the plasma 15 minutes after administration and the proportion of this which was "bound" to serum-globulin (fig 4) After immunisation five of the six animals showed an increase in insulin responsiveness, but the mean change was not significant at the 5% level None seemed to have developed a measurable titre of insulin-neutralising activity (table IV)

TABLE II—PARTIAL CORRELATIONS AMONG INSULIN RESPONSE, SERUM RETENTION AND GLOBULIN-BINDING OF INSULIN IN TREATED DIABETIC PATIENTS

—		r	P
Insulin response	globulin-binding of insulin	−0 3762	> 0 10
Insulin response	serum retention of insulin	+0 1130	> 0 10
Globulin-binding	serum retention of insulin	+0 7493	<0 05

TABLE III—EFFECTS OF ACTIVE IMMUNISATION ON INSULIN METABOLISM

Animal no	Insulin response (area, arbitrary units)		Insulin retention (% of dose remaining in plasma at 15 min)		Globulin-binding (% of plasma insulin bound to γ-globulin)		Hæmagglutinating antibody (titre)
	Before	After	Before	After	Before	After	After immunisation*
1	705	1145		19	2 9	22 1	512, 256
2	112	603	8	86	5 5	73 5	512, 512
3	1288	2299	12	33	3 9	22 4	512, 256
4	530	1070	11	18	5 4	29 1	512, 256
5	735	227	8	51	5 4	82 1	256, 512
6	885	915	12	33	4 7	52 0	512, 512

* Determinations were done on aliquots of serum taken 4 days apart

Passive Immunisation of Rabbits to Insulin

Globulin-binding and the disappearance rate of insulin were studied in five rabbits 36–40 hours after passive immunisation with insulin-binding serum obtained from diabetic patients Such treatment resulted in a variable increase in globulin-binding of ^{131}I-insulin but did significantly slow the removal of insulin from the circulation (fig 3)

TABLE IV—ASSAY FOR INSULIN-NEUTRALISING ACTIVITY IN RABBIT SERUM BEFORE AND AFTER IMMUNISATION WITH INSULIN

Animal	Insulin dose (milliunits)			
	2		6	
	Before	After	Before	After
1	36	38	50	53
2	16	23	25	46
3	25	12	53	29
4	11	27	25	61
5	22	42	41	76
6		21		39

Values represent the mean fall in blood-sugar (mg per 100 ml) in five mice 45 minutes after injection of serum-insulin mixture The fall in blood sugar produced by insulin alone was
2 milliunits, 13 ± 10 mg
6 milliunits, 30 ± 15 mg

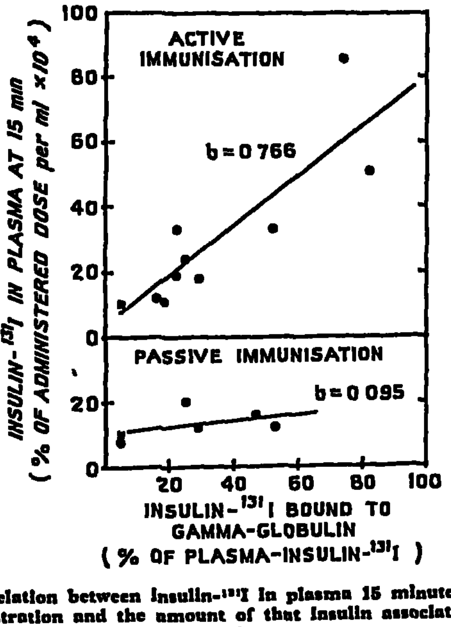

Fig 4—Relation between insulin-^{131}I in plasma 15 minutes after administration and the amount of that insulin associated with γ-globulin on paper electrophoresis

Upper results of 9 tests in six rabbits actively immunised by repeated injection of insulin Lower Results in five rabbits passively immunised by infusion of serum-proteins from insulin-treated diabetic patients Symbol (▪) in lower left corner represents mean normal values

Location of Insulin-binding Globulin

Characteristic examples of the results obtained on fractionation of serum-insulin-^{131}I mixtures by moving-boundary electrophoresis are shown in table V When serum from a non-diabetic subject was used, the insulin moved principally with the albumin and α_1-globulin With serum from an insulin-treated diabetic patient, the insulin was associated principally with the β-globulin, although on paper electrophoresis it apparently moved with γ-globulins Addition of excess insulin to diabetic serum resulted in movement of radioactivity with all protein fractions, when the serum-insulin mixture was passed through a powdered cellulose column (15 × 0 8 cm) most of the radioactivity remained on the column, and that which passed through the column with the serum showed the expected association with β-globulin on subsequent free electrophoresis These results confirm by boundary

TABLE V—DISTRIBUTION OF INSULIN-^{131}I IN SERUM AFTER ELECTROPHORESIS

—	Albumin	α_1	α_2	β	γ
Normal serum	58	17	5	16	3
Diabetic serum	3	4	3	83	7
Diabetic serum + excess insulin	17	27	31	20	2
Diabetic serum + excess insulin passed through cellulose column		17	8	65	9

Values represent percentage of total serum activity electrophoresis the results obtained with paper electrophoresis (Berson et al 1956) and alcohol fractionation (Berson and Yalow 1957)

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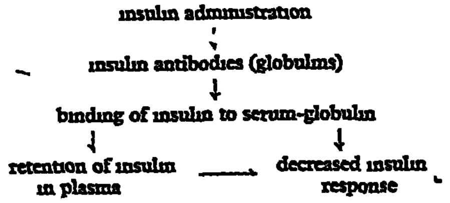
[3] Dr E R Arquilla and Dr A B Stavitsky kindly carried out these tests

Discussion

The hypothesis under examination may be expressed diagrammatically thus


insulin administration
insulin antibodies (globulins)
binding of insulin to serum-globulin
retention of insulin in plasma
decreased insulin response

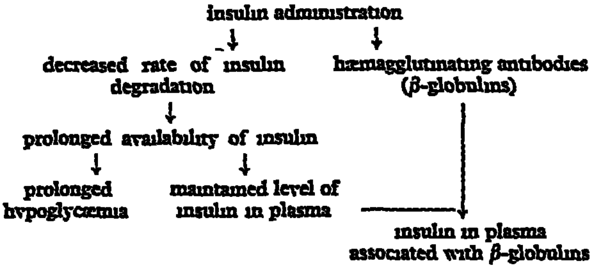
Diabetic patients previously treated with insulin had less response to insulin than diabetics who had comparable impairment of carbohydrate tolerance (t½G the same in both groups) but had not been treated with insulin This finding is compatible with the above hypothesis However, contrary to what might have been expected, there was no apparent correlation between insulin response and degree of binding of insulin to serum-globulin Furthermore, the untreated subjects were for the most part newly discovered diabetics, and possibly they would have shown a further impairment of insulin response with time alone In addition, since diabetes is not a disease entity of single ætiology, there are undoubtedly several unknown and uncontrolled factors affecting insulin responsiveness in groups of patients such as these

The likelihood of such variation was less in the rabbit experiments, in which normal animals were used Here it is evident that administration of insulin led to the development of hæmagglutinating antibodies, to globulin-binding of insulin, and to delayed disappearance of insulin from the circulation Except for one animal, however, there was no evidence of diminution of response to insulin, and indeed there may have been an increased response Moreover, after immunisation there was no evidence of circulating insulin-neutralising activity It therefore appears that neither retention of insulin in the plasma, binding to serum-globulin, nor the presence of hæmagglutinating antibodies to insulin inhibits the action of insulin

The low incidence of insulin resistance in these animals is comparable to that obtained by Lowell and Franklin (1949) with similar methods in a larger group of animals Moloney and Coval (1955) were also unable to produce insulin-neutralising antibodies in the rabbit.

The infusion into rabbits of serum-proteins from treated diabetic patients resulted in "passive transfer" of globulin-binding of insulin, but not of retention of insulin in the circulation Hence we may conclude that binding of insulin by globulin is not the cause of insulin retention

The results described are not compatible with the hypothesis as stated above, but are compatible with an alternative hypothesis This is that long-continued administration of insulin results in two abnormalities (*a*) a primary decrease in the rate of insulin degradation, leading to passive retention of insulin in the circulation and to a prolonged insulin effect, and (*b*) the appearance of circulating antibodies which form with insulin a loose complex which does not inhibit either degradation or the association of insulin with tissues, and consequently does not inhibit the response to insulin or affect the rate of its removal from the circulation The latter phenomenon does not conform to the generally accepted idea that antibody increases the rate of removal of antigen from the circulation, and suggests that the insulin-binding globulin may not in fact function as an antibody in the usual sense These relationships may be presented schematically


insulin administration
decreased rate of insulin degradation
hæmagglutinating antibodies (β-globulins)
prolonged availability of insulin
prolonged hypoglycæmia
maintained level of insulin in plasma
insulin in plasma associated with β-globulins

The decrease in the rate of degradation may be due to a humoral factor, since plasma from patients showing insulin retention can apparently inhibit insulin degradation in vitro (Welsh et al 1956)

Such a hypothesis is not incompatible with certain diabetics having insulin resistance, of varying degree, related to the formation of antibodies, but such antibodies appear to differ from those which are only the result of repeated administration of insulin

The electrophoretic analyses confirm the finding of Berson and Yalow (1957) that the "insulin-binding protein" is a β-globulin rather than a γ-globulin When the binding capacity of this protein was reached, excess insulin travelled with other proteins in a non-specific manner, exposure to cellulose removed the "excess" insulin, so that the remainder had the expected distribution pattern It must be emphasised that the actual specific activity values obtained for γ-globulin and albumin may be considered accurate, but the remainder, being obtained by difference, are only approximations

Conclusions

1 Diabetic patients previously treated with insulin had less insulin response than diabetic patients who had not been previously treated The insulin response was apparently not related to the degree of globulin-binding of insulin or to the degree of insulin retention in the circulation

2 Repeated injection of insulin into normal rabbits led to the development of hæmagglutinating antibodies to insulin, the removal of insulin from the circulation was altered, and binding of insulin to serum-globulin was demonstrable There was no evidence of a decrease in the hypoglycæmic response to insulin or of the presence of anti-insulin activity in the serum

3 Infusion, into normal rabbits, of serum obtained from insulin-treated diabetics led to the globulin-binding of insulin but did not alter the rate of insulin removal

4 It is concluded that insulin-binding antibodies and hæmagglutinating antibodies are not responsible for decreased responsiveness to insulin or for its slower removal from the circulation

5 Moving boundary electrophoresis indicates that the insulin-binding antibodies are β-globulins

REFERENCES

Arquilla, E. R , Stavitsky, A B (1956) *J clin. Invest* 35, 458
Berson, S A , Yalow, R S (1957) *ibid* 36, 642
— — Bauman, A , Rothschild, M A , Newerly, K (1956) *ibid* 35, 170
Colwell, A R , Weiger, R. W (1956) *J lab clin Med* 47, 844
De Filippis, V , Iannocone, A (1952) *Lancet*, i, 1192
Heller N , Kalant, N , Hoffman, M M *J lab clin Med* (in the press)
Lowell, F C , Franklin, W (1949) *J clin Invest* 28, 199
Moloney, P J Coval M (1955) *Biochem J* 59 179
Sehon A H , Kaye, M , McGarry, E., Rose, B (1955) *J lab clin Med* 45, 765
Somogyi, M (1952) *J biol Chem* 185, 19
Welsh, G W , Henley, E D , Williams, R H , Cox, R. W (1956) *Amer J Med* 21, 337

MONILIAL PERITONITIS AS A COMPLICATION OF PREOPERATIVE INTESTINAL STERILISATION

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MONILIAL peritonitis seems to be very rare We have only been able to find one published case (Reynell et al 1953) The patient was a man, aged 49, who was treated with corticotrophin and aureomycin for suspected periarteritis nodosa and had a duodenal ulcer After three days' treatment peritonitis developed, and the patient died four days later Necropsy revealed a perforated duodenal ulcer and peritonitis, *Candida albicans* was cultured from the peritoneal cavity It was assumed that the chemotherapy had changed the intestinal flora in favour of *C albicans*, which entered the peritoneal cavity through the perforated ulcer and caused the infection

We have observed a similar case, which is described below

Case-report

A girl, aged 4 years, had had sluggish bowel movements since birth For six months before admission her constipation increased in severity, becoming associated with abdominal distension, attacks of pain, and vomiting Radiography having revealed megacolon, an operation was advised From the day before operation phthalylsulphathiazole 3 g six times daily for two days and duostreptomycin 1 ml thrice daily for seven days were given orally together with procaine penicillin 200,000 units daily

Operation revealed segmental dilatation, mainly of the transverse colon, the lower portion of the descending colon, the sigmoid, and the rectum being normal The colon was resected from 8 cm above the ileocæcal valve to the lower portion of the descending colon, with end-to-end anastomosis

Postoperative course—The immediate postoperative course was uneventful, but on the eighth day pyrexia developed, for which reason the dosage of penicillin was increased to 1,000,000 units twice daily On the eleventh postoperative day increasing pneumoperitoneum, with distended abdomen but without peritoneal reactions, was noted It was supposed to be due to a small leakage at the site of the anastomosis, but, owing to the surprisingly good general condition of the patient and the absence of signs of peritonitis, further developments were awaited During the next few days the patient began to whimper, the abdominal distension increased, and incipient paralytic ileus developed, but signs of peritonitis were still absent (temperature 38 2 C)

Reoperation on the sixteenth postoperative day revealed a peculiar diffuse inflammation with dense adhesions of the intestines The picture did not resemble that of purulent peritonitis, pus was absent, but the intestines were covered by dry fibrinous flakes The anastomosis was found to be leaking slightly, so the anastomosis was transformed into a colostomy Culture of material from the peritoneal cavity yielded a heavy growth of *C albicans* but no bacteria

Postoperatively gastric paralysis developed, but intestinal function was resumed on the fourth postoperative day Pus discharged from the colostomy for some time, cultures of it produced *C albicans*, proteus, and enterococci Chemotherapy with various drugs led to gradual improvement, and the patient was discharged cured four months after the first operation

Discussion

It can scarcely be doubted that the chemotherapy given immediately before and after the first operation had changed the intestinal flora, with the result that it mainly consisted of *C albicans*, which entered the peritoneal cavity through the leaking anastomosis and caused the peritonitis

It is well known that various combinations of chemotherapeutic agents and antibiotics used for so-called intestinal sterilisation before major abdominal operations only remove the intestinal bacteria, the fungi normal to the intestines continuing to proliferate until they ultimately constitute the greater part of the intestinal flora Although fungi are usually considered to be of low virulence, they may, as in the present case, give rise to severe infection It must be assumed that the peritoneum was not contaminated during the operation, but that the intestinal leakage persisted for some time, during which large amounts of *C albicans* entered the peritoneal cavity

The chemotherapy used has no effect on the fungi It may therefore seem strange that the patient, who had severe peritonitis, recovered However, the human body usually has a strong resistance to *C albicans*, and the peritonitis presumably developed only because fungi had constantly entered the peritoneal cavity before the colostomy was established

Cases of this type are undoubtedly rare, but the case reported here shows that preoperative intestinal sterilisation is not without hazards

Summary

A case of monilial peritonitis in a girl, aged 4 years, whose colon had been resected for megacolon, is reported It is assumed that preoperative chemotherapy to sterilise the intestine changed the intestinal flora, with the result that it mainly consisted of *C albicans*, which penetrated into the peritoneal cavity through a leaking intestine

REFERENCE

Reynell, P C., Martin, E A, Beard, A W (1953) *Brit med J* 1, 919

EFFECT OF A LAMINARIN SULPHATE (LM 46) ON BONE GROWTH

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LAMINARIN is a polysaccharide consisting of approximately 20–30 glucose units joined by β–1 3 linkages, and occasionally a β–1 6 linkage (Connell et al 1950, Percival and Ross 1951, Friedlaender et al 1954) It is obtained from certain brown seaweeds and occurs in two forms—" soluble laminarin " from *Laminaria digitata*, and " insoluble laminarin " from *L cloustoni* The latter can be sulphated to produce soluble compounds with varying numbers of sulphate groups per glucose unit Several of these products have been examined previously for anticoagulant activity and toxicity, both of which increase with sulphation (Adams and Thorpe 1957)

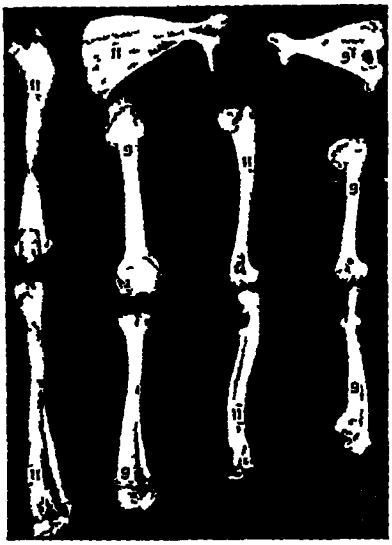

Fig 1—Bones (a) from rabbit (9) treated with LM 46 30 mg per kg intravenously daily for 24 days, (b) from control rabbit (11) which received heparin 10 mg per kg intravenously daily for 23 days

Note small size of bones from rabbit treated with LM 46 and considerable deformity of bone ends, especially at knee and shoulder

We have studied in more detail other laminarin sulphates prepared from laminarin derived from *L cloustoni*, one of which—LM 46—was more toxic and more highly sulphated than the others Initial experiments revealed that this compound had an anticoagulant activity equivalent to 33 heparin units per mg when tested by the sulphated whole blood method (Adams and Smith 1950) The acute intravenous L D 50 to mice was approximately 1500 mg per kg, but the "anaphylactoid" reaction (Walton and Ricketts 1954) was produced in guineapigs by intravenous doses of 100 mg per kg body-weight These results are similar to those reported for laminarin sulphate K (Adams and Thorpe 1957) However, on protracted dosing to rabbits, guineapigs, and rats, LM 46 produced effects which were quite different from those reported for other laminarin sulphates, and which we believe have not been recorded previously for sulphated polysaccharides We give here a preliminary report of these findings, particularly of the skeletal changes

Methods

LM 46 was administered subcutaneously or intravenously to rabbits, guineapigs, and rats on 5 days of each week for 2–9 weeks Rabbits received 15, 30, and 60 mg per kg body-weight, rats 15 and 30 mg per kg, and guineapigs 15 mg per kg daily The ages of the animals at the start of the experiments were rabbits 6–8 weeks, rats 3–4 weeks, and guineapigs 6–8 weeks Control animals, littermates in the case of the rabbits, received a dose of heparin equivalent in anticoagulant activity to the laminarin sulphate

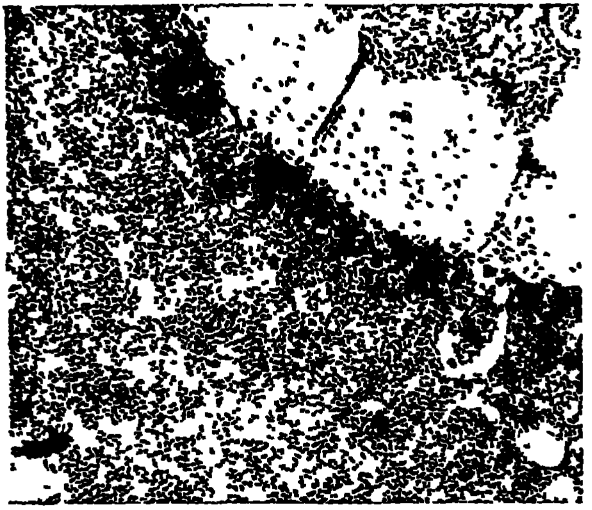

Fig 2—Epiphyseal plate at lower end of femur of rat treated for 49 days with laminarin sulphate LM 46 at 15 mg per kg subcutaneously daily (Hæmatoxylin and eosin ×75)

There has been complete arrest of maturation of cartilage with consequent failure of endochondral bone formation in metaphysis

When the animals became moribund they and the heparin controls were killed with intravenous barbiturate, and soft tissues and long bones were taken for histological examination The remainder of the skeleton was retained for preparation of dry bone specimens

Results

In all animals there was a pronounced loss of weight after prolonged dosing, and they seemed very frail both in appearance and when handled The rabbits and guineapigs had a white discharge in the eyes

The most interesting effects, however, were the skeletal abnormalities, which were most striking in the rabbits,

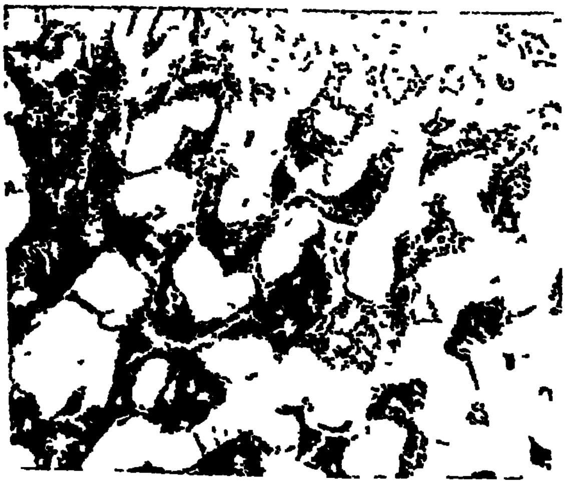

Fig 3—Epiphyseal plate at lower end of femur of control rat treated with heparin at 10 mg per kg subcutaneously daily for 49 days (Hæmatoxylin and eosin ×75)

Endochondral ossification is proceeding normally, resulting in rich network of newly formed bone trabeculæ in metaphysis

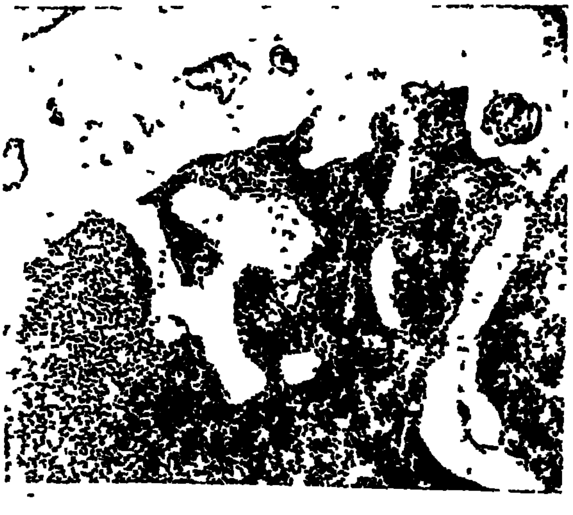

Fig 4—Lower epiphysis of same femur as in fig 2. Bone trabeculae normally present have been almost completely removed (Hæmatoxylin and eosin ×75)

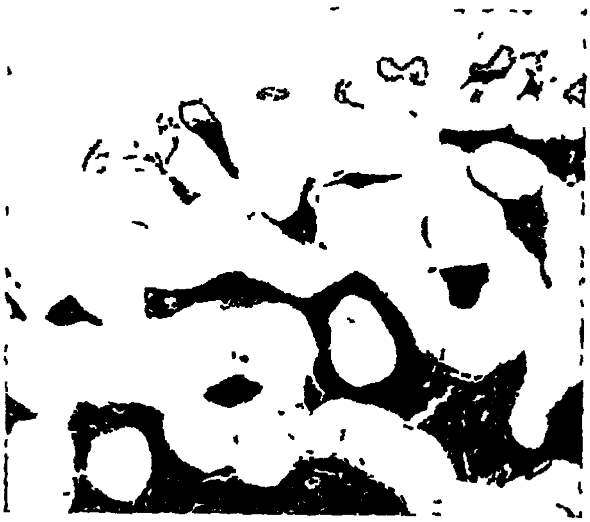

Fig 5—Lower epiphysis of the same femur as in fig 3 Rich network of bone trabeculae is in striking contrast to that in fig 4 (Hæmatoxylin and eosin ×75)

sometimes after only a few days of dosing Initially, the carpal joints became knobbly, and later the condition worsened until these joints were grossly abnormal and caused pronounced splaying of the feet either inwards or outwards Later there was weakness in the pelvic region which sometimes developed into complete paralysis In some animals the femur fractured

In rats the 15 mg per kg dose produced its effects more slowly than in the rabbit, and the forelimb distortion was less obvious, but there was definite weakness in the pelvic region, and distinct kyphosis developed In guineapigs the effects were similar to those in the rabbit, but they appeared more gradually

Both macroscopically (fig 1), and histologically the changes were greatest at the growing ends of the long bones In guineapigs and rats normal maturation of the cartilage cells in the epiphyseal plate was lacking, and there was deficient invasion of this zone by capillaries from the adjacent marrow There was, in consequence, almost complete absence of new bone trabeculæ in the metaphysis (figs 2 and 3) There was simultaneous loss of bone trabeculæ in the epiphysis (figs 4 and 5), which, in extreme cases, was reduced to a shell of cortical bone enclosing the vascular marrow The epiphysis then collapsed (fig 6), and this resulted in pronounced deformity of the articular surface with hæmorrhage and necrosis of the epiphyseal marrow Similar but less severe hæmorrhages and necrosis were sometimes seen in the metaphysis In rabbits the maturation of the cartilage cell columns appeared normal, but very little bone was deposited on the cartilaginous trabeculæ despite striking hyperplasia of osteoblasts in the metaphysis Necrosis commonly overtook these defective bone trabeculæ

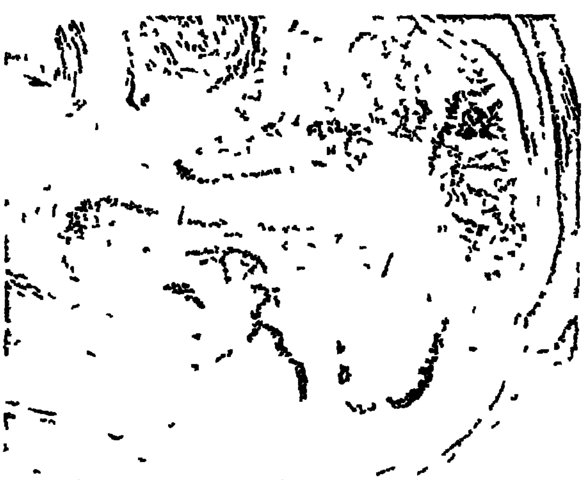

Fig 6—Shoulder-joint of rabbit treated for 24 days with laminarin sulphate LM 46 at 30 mg per kg intravenously daily (Hæmatoxylin and eosin ×3 approx)

Head of humerus has collapsed owing to absorption of bone trabeculæ in head, and defective endochrondal bone formation in metaphysis Epiphyseal plate is itself disrupted into several fragments

In addition to the bone lesions all the animals showed accumulation of metachromatic material in the reticulo-endothelial system and in the proximal convoluted tubules of the kidneys

Discussion

The bone lesions that develop after repeated injections of this particular laminarin sulphate appear to depend primarily on disturbance of the endochondral bone formation that normally takes place on the diaphyseal side of the epiphyseal cartilage In rats and guineapigs the normal sequence of maturation of the cartilage cells is impaired, and this is associated with virtually complete absence of the vascular invasion that normally precedes the actual deposition of bone on the newly formed tongues of calcified cartilage In rabbits it is apparently this deposition of bone which is impaired It is not at present possible to say how these disturbances are brought about by the laminarin sulphate, but its structural similarity to chondroitin sulphate suggests that it might be acting by interfering with the normal metabolism of chondroitin sulphate, especially at sites where the turnover-rate of the normal polysaccharide is high There is, moreover, some evidence that the effect of this laminarin sulphate may be shared by other sulphated polysaccharides Thus, L L Coleman (cited by Regelson and Holland 1958) found osteoporosis in rabbits receiving injections of either polyethylene sulphonate or heparin, and fractures in cholesterol-fed rabbits receiving repeated injections of heparin have been reported by Gillman and Naidoo (1957) A study of the mechanism by which these sulphated polysaccharides produce bone lesions should provide valuable information about the normal processes of endochrondral bone formation

Addendum

Since this paper was prepared H C Hint and A W Richter (*Brit J Pharmacol* 1958, **13**, 109) have reported similar findings in the rabbit following the chronic administration of dextran sulphate They do not, however, refer to forelimb deformities such as we have reported here, and which we have also found following the administration of clinical-size dextran sulphate We have noted that forelimb deformities occur only in very young rabbits, and for that reason used animals aged 6–8 weeks Hint and Richter used animals 5–6 months old—an age at which we would not expect the forelimb deformities to be obvious, except perhaps at necropsy

REFERENCES

Adams, S S, Smith, K L (1950) *J Pharm Pharmacol* 2, 836
— Thorpe, H M (1957) *ibid* 9, 459
Connell J J Hirst, E L, Percival, E G V (1950) *J chem Soc* p 3491
Friedlaender, M H G, Cook, W H, Martin, W G (1954) *Biochim biophys Acta*, 14, 136
Gillman, T Naidoo, S S (1957) *Nature, Lond* 179, 904
Percival, E G V, Ross, A G (1951) *J chem Soc* p 720
Regelson, W, Holland, J F (1958) *Nature, Lond* 181, 46
Walton, K W, Ricketts, C R (1951) *ibid* 173, 31

Preliminary Communication

A SINGLE-PUMP BUBBLE OXYGENATOR

THE deliberate foaming of blood as a means of oxygenation was described by Schroeder[1] in 1882, but the principle was not applied to extracorporeal circulation until 1956 The description by De Wall et al,[2] of a disposable bubble oxygenator coupled with the fixed-low-flow principle, developed in their cross-circulation work, has been followed by a series of modifications of the apparatus [3-6]

We record here some further modifications which have evolved in the course of our experimental [7 8] and clinical experiences and which have been dictated by the need for simplicity and economy

APPARATUS

In the original circuit[2] the venous blood was aspirated from the venæ cavæ directly to a 'Sigmamotor' pump With such aspiration, adherence of the caval walls to the orifices of the catheters often interfered with venous return We have got over this difficulty by using gravity drainage into a venous reservoir—which has incidentally simplified adjustment of the pumps during bypass We have found it possible to eliminate the venous pump and to rely on gravity to return the venous blood to the reservoir and thence to the oxygenator column The whole apparatus is lowered so that the top of the oxygenator column is below the level of the right atrium (fig 1)

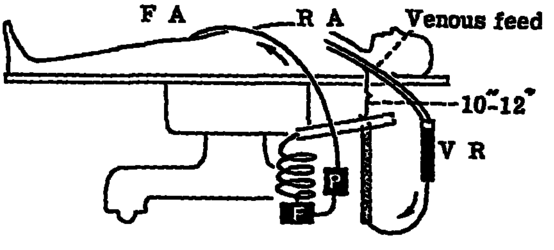

Fig 1—Showing the relation between the pump oxygenator and the patient

CARDIOPULMONARY BYPASS SURVIVAL EXPERIMENTS USING GRAVITY DRAINAGE AND ONE PUMP

Dog	Weight (kg)	Flow (ml per min)	Bypass (mins)	Blood-pressure (mm Hg)	Survival-time
1	11·5	1200	14		12 hours
2	13·0	1500	24	110	8 days (killed)
3	9·8	500	22	40–80	7 days (killed)
4	10·5	600	20	45–100	8 days (killed)
5	8·9	550	20	40–100	5 days (died)
6	9·0	600	20	40–90	12 hours
7	13·3	700	20	70	4 hours
8	9·9	530	20	40–90	6 days (killed)
9	9·0	450	20	60	7 days (killed)
10	9·7	500	20		6 days (killed)

Elimination of the venous pump removes a source of blood trauma

Under experimental conditions in our laboratory, a single T6S sigmamotor pump set at an output of 1 litre per minute, with a priming volume of 1 litre of dog blood, will produce 50–70 mg of free hæmoglobin per 100 g of blood after 1 hour With a priming volume of 2 litres, and a flow of 2 litres per minute for 1 hour, it will produce 200–250 mg

To reduce the blood damage we have substituted for the sigmamotor pump a commercially available British-made 'Mono' pump, which utilises the archemedian screw principle The use of this pump has a sound theoretical basis[9] and it has given excellent results in our hands (see table)

It gives a continuous flow of up to 6 litres per minute and can maintain a constant output against a head of pressure of 90 feet of water A standard production model B15 has been used, but sterile assembly of the unit has introduced some difficulties The manufacturers are now developing a unit which can be easily autoclaved and assembled At present the pump is driven by a $^1/_4$ h p single-phase 240-volt A C motor of 960 r p m through a Kopp 'Variator' to give a range of output from 700 to 5000 ml per minute

The coronary-sinus return is collected in an evacuated reservoir of conventional type maintained at a negative pressure of 3 cm of mercury by a separate suction pump From the bottom of this reservoir the blood is pumped by a hand-operated roller pump to the venous reservoir The circuit is primed by sucking filtered blood into the coronary-sinus reservoir and pumping it into the venous reservoir (fig 2)

The oxygenator column has an internal diameter of

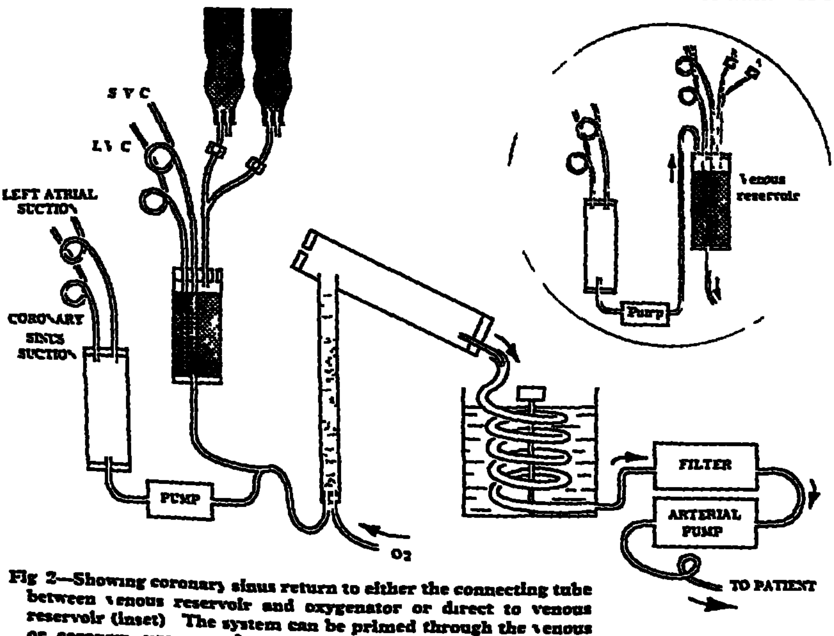

Fig 2—Showing coronary sinus return to either the connecting tube between venous reservoir and oxygenator or direct to venous reservoir (inset) The system can be primed through the venous or coronary-sinus reservoirs. The lead from coronary-sinus reservoir to external suction is not shown

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1 Schroeder, v N *Arch exp Path Pharmak* 1882 15, 364
2. De Wall, R A, Warden, H E., Gott, V L, Ziegler, N R, Varco, R K Lillehei, C. W *Surg Clin N Amer* 1956 36, 1025
3 Gammelgard, R A, Husfeldt, E, Therkelsen, F *Acta chir scand* 1957 112 439
4 Gott, V L, De Wall, R A, Paneth, M, Nazhi Zuhdi, M., Weirich, W, Varco, R, Lillehei, C W *Thorax*, 1957, 12, 1
5 Cooley, D A, Belmonte, B A., Latson, J R, Pierce, J F *J thorac Surg* 1958 35, 131
6 Giannelli S, Jr, Molthan, N F, Best, R J, Dull, J A, Kirby, C K *ibid* 1957, 34, 563
7 Taylor, D G *Guy's Hosp Rep* 1958, 107, 100
8. Taylor, D G Cavanagh, J B Unpublished.

9 Hall J E, James, P A, Lucas, B G B, Waterson, D J *Thorax*, 1958, 13, 1

$1^{1}/_{2}$ in and the tube connecting it to the venous reservoir has an internal diameter of $^{1}/_{8}$ in

RESULTS

This simplified circuit has been used on ten dogs and there have been seven survivors In the first experiment a filter was not used but in the remainder one has been incorporated in the base of the helix The amount of debris found on the filter at the end of each bypass has varied considerably, for no apparent reason In the sixth experiment there was insufficient blood to prime the circuit and the operating level in the helix was around 200 ml There should be at least 1 minute's flow volume in the helix to reduce the possibility of micro-bubbles being drawn into the arterial line The seventh dog died from a pulmonary embolus arising from the right atrial appendage A clamp had been applied to the appendage and two purse-string sutures inserted 20 minutes before heparin was given

The apparatus used in clinical cases has now been modified similarly Two patients (a tetralogy of Fallot and a ventricular septal defect) have been operated on using the modified oxygenator circuit and a single sigmamotor pump The patient in whom the ventricular septal defect was closed is alive and well The patient with tetralogy of Fallot died 24 hours after attempted complete correction Consciousness was regained and death is not attributed to the perfusion technique

DISCUSSION

Doubts have been expressed about the safety of bubble oxygenation,[10,11] but in view of its successful clinical application we decided to retain this technique while simplifying the circuit

The substitution of gravity drainage for pump suction immediately removed one of the main sources of anxiety during bypass While the venous pump was always carefully balanced against the arterial, frequent variations in the venous return necessitated continual adjustment of the venous pump With gravity drainage and elimination of the venous pump the circulation adjusts itself automatically and in a much shorter time

The hæmolysis caused by the sigmamotor pump, and its limited output, prompted the trial of the Mono pump which has a low hæmolysis factor, is cheaper, and is readily obtainable in this country Its range of output is adequate for all prospective bypass cases and its constant-flow delivery is a superior means of returning blood to a patient through a narrow cannula A pulsatile flow results in peaks of high pressure in the tubing between pump and patient at the top of the input stroke, and at the same time the jet injected through the cannula into the femoral artery gives rise to considerable turbulance All these factors must be harmful to the blood and seem unnecessary when one considers that at the site of oxygen exchange in the capillaries the pulsatile flow has been lost

SUMMARY

A simplified circuit for a bubble oxygenator is described Blood from the venæ cavæ is conducted to the base of the oxygenator by gravity, so that a venous pump is unnecessary For the arterial return a 'Mono' pump is used

We would like to acknowledge the cooperation of Mono Pumps Ltd, who supplied a pump for protracted trial, of Allspeeds Ltd (Oakenshaw Works, Clayton-Le-Moors, Accrington, Lancs), who provided a Kopp variator, and of the department of medical illustration, Guy's Hospital The two patients were operated on by Sir Russell Brock, whose continued support and encouragement have made this work possible

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[10] Dieah, G, Flynn P J, Marable, S A, Molder, D G Schmutzer K J, Longmire W P, Jr, Maloney, J V Surgery, 1957 42, 67

[11] Jordan, P, Jr, Tolstedt, G E, Beretta, F I ibid 1958, 43, 266

Reviews of Books

Doctor and Patient in Soviet Russia

Mark G Field, PH D, with a foreword by Paul D White, M D Cambridge, Mass Harvard University Press London Oxford University Press 1958 Pp 266 40s

Dr Field has spent only a month in Russia, but at the Russian Research Center at Harvard University he has made a long study of Soviet books and journals, has interviewed many doctors who have left Russia, and has analysed answers to a questionary addressed to 1650 former Soviet citizens His book is described as a study not of Soviet medicine but in the sociology of the medical profession, but as such it is the most penetrating commentary on medical Russia that we have seen Soviet medicine provides, he says, almost the extreme example of interference with the doctor's work Since the revolution Russia has been a mobilised society in which (as in war-time here) priorities at all levels have been laid down by the leaders Medicine had to be controlled in order that its practice should fit the aims of the regime, and, so long as the chief aim was intensive industrial production, doctors were under particular pressure in their certification of sickness The resistance of doctors to State pressure was weakened by abolishing their professional organisations, by indoctrination of students, and by reducing the doctor's prestige and standard of living Dr Field notes a striking resemblance between the position of doctors in Russia and that of schoolteachers in the U S A Admitting the advantages of central direction, he describes the harm done by red tape, and by the setting of " norms " in practice, and he also describes the gross differences in the kind of medical care given to different classes Yet, after forty years' vicissitudes the tradition of personal service has survived in the Russian doctor, comparing him with his German colleague, a refugee said that, though he has no complex equipment, he is " much warmer and more serious and, in the end, much better for the patient " Though, as Dr Field fully realises, the evidence of refugees from the U S S R will scarcely be unbiased, of 617 émigrés questioned in New York, 50% preferred Soviet medical arrangements and only 18% the American " In the Soviet Union ", said one, " the doctor is the slave of the State In America he is the slave of the dollar "

In many ways a formidable indictment of the Soviet system, this book is scrupulously fair

Advances in Virus Research

Vol 5 Editors K M Smith, virus research unit, Agricultural Research Council, Cambridge, M A Lauffer, department of biophysics, University of Pittsburgh, Pennsylvania New York Academic Press London Academic Books Pp 376 76s

The fifth volume is very much up to the standard set by its predecessors, and continues to provide authoritative reviews on different aspects of virus research The chapter by G S Stent on Mating in Reproduction of Bacterial Viruses is outstanding, and the synthesis of ideas presented in his review is likely to have a big influence on future research There are three good reviews on virus groups—J B Brooksby writes on foot-and-mouth disease, H A Wenner on the psittacosis group of viruses, and Ph L'Héritier on the hereditary virus of drosophila G Bertani tackles an important topic—lysogeny—in a stimulating way F Fulton writes authoritatively on complement fixation as applied to virology, and Anne Buzzell and M Hanig wrestle with influenza-virus hæmagglutination

THE LANCET

LONDON 20 SEPTEMBER 1958

The Professional in Russia and China

In our type of western society, professions are important. Even when most of their members are working in State organisations, the professions remain independent of Government and continue to set their own standard, exerting their corporate influence not only in their own interest but in that of the public, as they see it. As a rule, work is better done by people who belong to a profession, accepting its restraints and responding to its ideals, and the present tendency of vocational groups to demand professional status should be encouraged as part of the natural development of our kind of community. But there is also, of course, a contrary tendency towards denigration of professions as no longer necessary or useful for people who have entered a "State service". Because of this, the professions could be seriously weakened even though structurally extant. There are warnings, perhaps, in the story of medicine in Soviet Russia, which has now well over 300,000 doctors but can be said to have hardly any medical profession at all.

In the book we review on p. 622 Dr Mark Field, of Harvard, describes the social history of the Soviet medical profession as "the history of the transformation of a self-conscious, independent, vocal, politically oriented, and militant corporate entity to that of a docile and politically inert employee group." The doctors of Tsarist Russia, "appalled by the poverty and the misery that surrounded them everywhere", were many of them ardent reformers, and after the February revolution of 1917 they began to put into practice plans by which medical care and public health would be financed publicly but controlled and supervised by the profession. But in October all such projects came to an end with the advent of the Bolsheviks, whose philosophy could not tolerate the exercise of power or influence by anyone other than the State. Step by step, the new Government abolished the professional organisations and deprived doctors of their corporate strength by putting them into a vast Medical Workers' Trade Union in which (though they have a section of their own) they were swamped by feldshers, nurses, and other ancillary medical personnel. The ancillaries, having belonged to the formerly "exploited" classes, were now encouraged to assume the leadership formerly claimed by the bourgeois-liberal doctors. Moreover, the medical trade-union was itself subordinate to the central committee of trade-unions, and since the early '30s this has been hardly more than an instrument of the Government. "Little trace", Field says, "was left of the medical profession as an organized, self-governing, social group or social force."

The "basic ethical universalism of medicine, which regards the sick individual as someone to be helped regardless of his station in life or class origins", was displaced, in the new Soviet medicine, by a "class" approach in medical care, as in housing, food, higher education, and other amenities, there was discrimination against people who were not party members or who did not belong to proletarian classes. Moreover, in a State which was on a war footing from its beginning, the interests of individual people came second to those of the community. Doctors should prevent disease, but, if they failed, they must at any rate do their utmost to prevent its interfering with production, and they were sometimes told that their first duty was to get as much work as possible out of their patients. Though this new sense of predominant duty to the community could scarcely be expected of people trained under the old regime, it was carefully inculcated into their successors, who now form the vast majority. Yet, strangely enough, the old medical tradition of personal service has survived. Despite official preference for workers' families, a high proportion of candidates for the medical schools come of middle-class parents who see in medicine a chance for their children to "help the people" without being directly involved with the regime or with politics.

Though no doubt most Russian doctors are generally in favour of the Socialist system which has modernised their country, Field produces evidence that less than a quarter are members of the Communist Party, and that most of these are administrators rather than clinicians. He speaks of a feeling among the others that party doctors "have somehow betrayed the profession by swearing allegiance to another group." He was told of a "sharp social split between party and non-party physicians, and that the latter tried as much as possible to avoid contact and involvement with the former even in professional matters."

Especially in former days, when labour legislation was more draconian, doctors concerned with certification of illness were exposed to severe strains: the authorities often expected them to put industrial production before health, whereas the patients expected them to be merciful and be their friends. With a style and standard of living little above that of most of the population, the doctor tended to identify himself with the patient and, as the "attorney of the poor", he was often able, by judicious use of the medical excuse, to "cushion and somewhat soften the impact of the system on the individual." Thus his work has become one of the adjustive mechanisms "that keep the social system going by reducing discontent, tension, and disaffection". Though the regime regard it as potentially dangerous because it escapes control, it is willing within limits to let him exercise his adjustive functions, and in fact "the physician's role of certification is a latent source of strength and flexibility in the system." It is an advantage to the regime that it has doctors who treat their patients as *their* patients—even at the risk of punishment. Similarly it is an advantage to the regime that, at the higher levels of medicine, some of the investigators have been less interested in official directives than in the progress of science outside their isolated country. There must be many who would agree with Field that "ideological controls imposed upon the medical profession add nothing to its efficiency, but rather detract from it by taking valuable time away from study and practice" Although (or perhaps because) there are no formal associations to band them together, there is a great deal of solidarity and cooperation among Russian doctors (other than party members), and now that political pressure on them has considerably abated, and international contacts seem rather easier, it will not be surprising if the profession regains some kind of corporate life

Whereas differences between Soviet Russia and other industrial nations seem to be steadily diminishing, the same may not be true of China The Russians began with a radically Communist revolution, but by successive concessions to expediency have achieved a national Socialist State now possibly in process of being liberalised The Chinese, learning by Russian experience, began with many compromises but now appear to be moving towards a more fundamental reorganisation of their society Among their compromises was the preservation of the Chinese Medical Association as the embodiment of the medical profession, and doctors from this and other countries who have visited China at the invitation of the Association have been heartened by finding that so many of its leading members have the same medical interests as themselves and apparently want to belong to the same medical world On the other hand, even last year, the issue was evidently in the balance The Chinese Medical Association has very close links with the Government, and official statements about the value of guidance by the Communist party have not been in line with Field's view (and ours) that "medicine, like other professions, is one in which the scientific approach must predominate and one which flourishes best in an atmosphere of free inquiry, scepticism, and the search for facts rather than doctrine, dogma, or political considerations" The Association's recent pronouncement on Anglo-American aggression in Arab countries [1] is depressing less because of its content than because it uses the stock phrases of Communist propaganda without so much as bothering to translate them into the more objective language more persuasive to doctors and scientists Even several years ago, when he made the observations recorded on p 633, Professor Gould formed the impression that in the Chinese struggle between science and dogma, science had already been defeated, and there is now more reason to fear that he is right If this fear is realised, however, we should still not make the mistake of underestimating what can be achieved by dogma, with technological aid, nor should we assume that what is thus achieved is necessarily inferior One of the greatest sociological experiments of our time, if not of all time, is beginning with the Chinese Government's new programme for dividing their population into huge communes in which men and women alike are to form a labour force disposable between the tasks of agriculture and industry [2] This scheme, which has the merit of avoiding the concentration of industry in cities with depopulation of the land, may take the Chinese much further towards Communism than the Russians have ever gone Beside so vast a social change, the loss of a profession, of professional ideals, and of the scientific attitude may seem a small one Nevertheless, in the long run, it would not be small at all

Fibrinolysin for Treatment of Blood-clots in Man

Blood-clots are not permanent structures, they may serve as a supporting framework for invading fibroblasts and capillary blood-vessels, but as these form new tissue the clot of fibrin disappears The process of getting rid of the fibrin—fibrinolysis—is now known to be brought about by a proteolytic enzyme and its precursors in blood tissues [1] The active fibrinolysin is named "plasmin", and this is present in blood in an inactive form called "plasminogen", plasminogen activators are present in blood, urine, and milk, trypsin can act as an activator There is also a system of proactivators, and one of the best-known of these is streptokinase Thromboembolism is still one of the serious causes of medical and surgical morbidity and mortality Once a clot has appeared, we prescribe anticoagulants in the hope of preventing further clots, and this indeed is the basis of the anticoagulant treatment of coronary thrombosis [2] But such treatment is like shutting the door after the horse has gone, tissue damage in the area blocked off by the original clot continues unchecked It would be better if we could remove the clot or recanalise the vessel as soon as possible, in addition to preventing extension or complication Accordingly attention has been given to fibrinolytic agents, and recent American reports suggest that a clinically useful fibrinolytic agent may have been prepared

Streptokinase was tested as a fibrinolytic agent [3], but streptokinase is not well tolerated and inhibitors were found commonly in blood Intravenous trypsin has been given a trial [4] it activates plasminogen and has some direct action on fibrin But here again there were snags antitryptic activity of plasma was found to be common, and the dose needed to produce an effect also interfered with other plasma-proteins, especially those concerned with blood coagulation Moser [5] has used a plasminogen prepared from the globulin fraction of human plasma-protein The plasminogen is activated to plasmin by streptokinase, which is subsequently removed, this active plasmin does not attack plasma-proteins other than fibrinogen and fibrin It had previously been shown [6] to remove clots produced experimentally in dogs and rabbits, and now Moser has reported on its use in 52 cases of thromboembolic disease in man, including 13 of cerebral thrombosis Lyophilised material was provided for clinical use, and it could be kept at −4°C for several months It was assayed in "fibrinolytic units", 1 F U is the amount of preparation which will change the turbidity of a standard fibrinogen-thrombin clot by 50% in ten minutes Clinical doses varied from 30,000 F U to 90,000 F U, the dose being increased as experience confirmed the safety of the substance, the lyophilised material was dissolved in 500-1000 ml of 5% dextrose solution and infused over two to four hours This material nearly always provoked a febrile reaction six to eight hours after the infusion, but any symptoms could be ameliorated by giving an anti-histamine drug, there was 1 case of generalised urticaria and 1 of local erythema There was no effect of any of the blood-coagulation tests Plasma-fibrinogen estimations showed that a small loss had occurred six hours after a dose of plasmin, but values were normal again in twenty-four hours There were no hæmorrhages even in patients having anticoagulant treatment. The fibrinolytic activity of the patient's plasma reached a maximum three hours after an infusion of plasmin; 30,000-50,000 F U raised the activity by 30%, and 70,000-90,000 F U produced a rise of 40%

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[1] *Chinese med J* August 1958
[2] *Manchester Guardian*, Sept 11, 1958, p 1 and 7

[1] Astrup, T *Lancet*, 1956, ii, 565
[2] *ibid* 1956 i 559
[3] Tillett, W S, Johnson, A J, McCarty, W R *J clin Invest* 1955, 34, 169
[4] Taylor, A, Overman, R. S, Wright, I S *J Amer med Ass* 1954, 155, 347
[5] Moser, K M *ibid* 1958, 167, 1695
[6] Grossi, C E, Clifton, E E *Surgery*, 1955, 37, 791

The best results were obtained with peripheral venous thrombophlebitis and pulmonary embolism 18 patients with deep venous thrombophlebitis were treated, most of them showed loss of heat and tenderness and decreased swelling within twenty-four hours, and within seventy-two hours the affected part returned to normal, the phlebitis did not recur when the patient got out of bed, and pulmonary embolism did not occur after the treatment. Experience with 12 cases of peripheral arterial occlusion was less encouraging, no patient was certainly relieved Of 14 patients with cerebral arterial occlusion there was maintained improvement in 4, transient improvement in 3, and no effect in 7, MOSER considers that from this small group no definite conclusions can be reached, but there was no evidence that any patient deteriorated, and the infusions could be given with safety In coronary thrombosis not enough patients have yet been treated to decide whether fibrinolysin will be useful SUSSMAN and FITCH[7] used the same preparation of plasmin as MOSER for the treatment of 3 patients with cerebral arterial occlusion In 1, with occlusion of an anterior cerebral artery, there was no effect. In another, aged 75, with hypertension, a left carotid arteriogram showed occlusion of the internal carotid artery just beyond the bifurcation of the common carotid artery, infusions of plasmin into the left carotid artery produced some clearing, but there was no clinical improvement. In the 3rd patient, who had occlusion of the middle cerebral artery, the block was relieved after plasmin infusions and there was some clinical improvement.

These results suggest that it is worth obtaining further experience with plasmin preparations, especially in the treatment of superficial and deep thromboses of leg veins The results in cerebral vascular disease have so far been disappointing, but in this group of disorders we have so little effective treatment that even not very promising methods are worth testing We still need more information on toxicity and on dosage, and we need to know whether fibrinolysin treatment should be followed by anticoagulant treatment, and for how long The American workers used a plasmin preparation that was commercially available, and it should not be difficult for a similar preparation to be made in this country

Decline of the Father-image

THE increase in crime during the past few months is worrying everyone, and rightly so, for, however critical one may be of Home Office statistics, the present crime-wave must be accepted as real and disquieting Yet its cause remains as obscure as the cause of crime itself From a psychological standpoint, it is easy to agree that a defect in the super-ego plays a large part in inducing criminal behaviour, and to accept FREUD's thesis that the super-ego is formed by parental and other authority, and is the repository of morals, prohibitions, conscience —in fact, of the sense of right and wrong But it is less easy to define the super-ego precisely, and still harder to pick out the influences which determine its function for better or for worse

Recent studies of this problem include two investigations using the thematic apperception test and have provided some tentative information (The test consists in asking the subject to tell a story round each of a series of pictures showing situations of differing emotional flavour) In Australia LYLE and GILCHRIST[1] compared the results it gave in groups of delinquent and normal boys, and in the United States JENSEN[2] applied it to groups of boys showing extremes of aggression and passivity The amount of aggression shown by all the boys did not greatly differ, but delinquent and aggressively antisocial boys related stories of "naked" aggression, whereas the normal and the passive groups "buffered" their fantasies of violence with just retribution, suicide of the malefactor, and mitigating factors such as stealing for a starving family or acting under hypnosis Analysis of stories according to some other criteria showed, surprisingly, no significant differences among the groups Thus references to murder, robbery, intra-family tensions, feelings of rejection, love, and loyalty, were evenly distributed between the groups But socially taboo aspects of sex, violence, and language were more common in the stories of the antisocial boys The difference between the groups was not in aggressiveness itself, but in their social attitude towards it the antisocial groups showed a lack of guilt-reaction—a defect, in fact, of the super-ego

These studies still leave open the reasons for this psychological defect, and people tend to put forward unverified suggestions which vary according to the ethical, religious, social, or political tub which they happen to be thumping But the reasons lately put forward by GALDSTON[3] deserve careful consideration He lays the blame on the decline of the family, and particularly the change of orientation within it. Writing of the United States, he describes the cult of "momism" and suggests that American society has swung from a patnarchal to a "matriarchoid" pattern—if we may hesitatingly use his neologism Modern technology and social circumstances have emancipated the mother to the point where she no longer needs to bake the bread, weave the cloth, feed the chickens, and teach the children, nor does she (as the father must) earn the money She is free to build up a dominating position within the family, and to wreak havoc on the children by overprotecting them and ousting father as the principal figure As he says

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[7] Sussman B J, Fitch, T S P J Amer med Ass 1958, 167, 1705

[1] Lyle, J G, Gilchrist, A A Br J med Psychol. January, 1958, p 51

[2] Jensen A R. Psychol Monogr 1957, 71, 13

[3] Galdston, I. Ment. Hyg 1958, 42, 229

> "The patriarchal family is rapidly disintegrating and in that process we are experiencing and witnessing a negation of those patterns, values and mores on which and by which our multi-millenial culture has been structured and buttressed Freud has taught us that the super-ego represents the introjected or incorporated father-image In the matriarchal family there is no conscionable father-image to introject"

GALDSTON's views on the matriarchy have some support from the GLUECKS' findings [4] that fathers of delinquents tend to be incompetent and lax in discipline Nearer home, the Metropolitan Police Commissioner [5] has reported a rise of 30%, during 1957, in young offenders between the ages of 17 and 21—many of whom, as war children, must have lacked even an incompetent father Those who agree with GALDSTON's observation that the structure of the family is changing may nevertheless be more cautious in laying responsibility for the change on the leisured mother During the Victorian age, for instance, thanks to maids rather than washing-machines, mothers of the middle classes probably had at least as much leisure as the mothers of today Yet paterfamilias retained his position as undisputed head of the family

However debatable this may be, few would disagree with GALDSTON when he points out that in the past the family was not merely a conglomeration of people but a working union Nowadays many of its duties and responsibilities have been taken over by other organisations, and the services for which the members of a family used to rely on each other have been reduced almost to vanishing-point Children, he reminds us, used to be an asset and from early years had their own useful place within the family But now they are regarded as a luxury, to be indulged in circumspectly They have no useful place, especially in urban life, and, save for their school work, have little to do and that little is of a "make-work" character

Nor does he neglect the importance of religion, surely the most super of super-ego forces The Church, he points out, was once the centre of art and culture, of music and community gatherings, of the healing and social services

> "Man is a creature that lives by values no less than by bread, and of late too many of his traditional values have been cast into doubt In the cataclysmic upheavals of two world wars, goodness, love, charity, mercy, truth, humility, brotherliness, have been violated and mocked There is current a highly organised, energetic and cunningly resourceful propaganda which makes the homely virtues and the religious persuasions and faiths of our fathers appear like a compound of neurotic anxiety, infantile delusions, political-economic naiveté and mean escapism Many who are caught in the tension field of this propaganda seek refuge in doctrinate bigotry, hence the resurgence of orthodoxy in morals and religion"

Much has been written about the so-called sick society (was it ever healthy?), and surely there can be no simple answer to the complex troubles of a complex civilisation Admittedly GALDSTON begs many questions (Would he, for instance, call English society *matriarchoid*?) But challenging views such as his are needed, if only to stimulate further social and anthropological studies A careful examination of the patient has long been held to be a useful prelude to effective treatment

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Annotations

FAMILY DOCTORS AT WORK

SINCE 1948 a great many words have been spoken and written about general practice under the National Health Service, many of them, perhaps too many, have suggested that the standard of care is deteriorating and have depicted the general practitioner himself as overworked, underpaid, and ill-supported in his work When the present is difficult it is tempting and natural to recall the past with indulgence and regret, but in its day the past probably had its difficulties too, and before accepting criticisms of general practice it is worth considering how many are founded on opinion and how many on fact

Prof R M Titmuss, who takes a reasonably optimistic view of the family doctor's opportunities and progress within the administrative framework of the N H S, reminds us that some of its keenest critics have failed to make explicit the criteria they have in mind, and have avoided concrete comparisons with the conditions of the 'thirties Expressions of opinion are never easy to rebut, especially when there are few facts with which to challenge them Statistics and controlled observations about general practice are scanty and incomplete, but such as they are, in Professor Titmuss' view, they offer little support to the critics He has summarised the 15 available surveys in a useful appendix to his stimulating American lectures, which have now been published in this country [1] The most reliable evidence in his view comes from figures collected by the Ministry of Health and the British Medical Association, and according to them the quantity of the family doctor's work has not increased since the 'thirties In 1938–39 he gave each of his panel patients 5 10 items of service, in 1949–50 he gave each of his N H S patients 4 62 items These figures do not suggest that patients are making unreasonable demands on their doctors Indeed N H S patients might reasonably be expected to have needed more items of service, for, unlike the panel patients, they include vulnerable groups of children and old people, yet the number of items has actually fallen There are, however, no figures for the demands of private patients, and since the introduction of the N H S some of these are probably turning to their doctor more freely Among these patients the doctor's work may have increased Even so Professor Titmuss considers that the level of total demand has remained relatively low

In other ways he thinks that the doctor's work has been lightened The doctor is making more use of hospital outpatient facilities, and of the services of district nurses for injections and dressings. Doctors are also more evenly distributed over the country, many have arranged voluntary rotas, and night visiting is becoming rarer. Nor does the N.H.S. patient seem to need as many certificates as some suppose (48 per 100 N.H.S. patients in 1953–54, compared with 139 per 100 panel patients in 1938–39).

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[4] Glueck, S Glueck E Unraveling Juvenile Delinquency New York, 1950

[5] Annual Report of the Metropolitan Police Commissioner, 1957 H.M Stationery Office

[1] Essays on 'The Welfare State" London George Allen & Unwin. 1958 Pp 232 20s

Quality is more difficult to assess than quantity, and standards of general practice cannot be judged on even the tenuous objective evidence available for quantity. But here, too, Professor Titmuss is unimpressed by over-facile jeremiads. The figures put before the Spens Committee, he reminds us, show that in the 'thirties too many practitioners were earning a miserable income, and in his view private practice was "less remunerative than most people were aware of then or imagine today." Most practices carried a burden of bad debts, and too many patients, oppressed by the cost, were reluctant to seek their doctor's help. Excellent as general practice often was, its benefits were often limited by accidents of wealth or locality, and families living in an industrial slum did not enjoy the same benefit as a family living in the village of Aysgarth.

His more buoyant assessment of general practice does not, however, mean that Professor Titmuss does not appreciate the problems that beset general practitioners today. He lays responsibility for many of these, however, not on the N.H.S., but on the impact of the physical sciences on medicine during the past forty years or so, and the increasing specialisation which these new complex techniques have demanded. Before 1948, Professor Titmuss points out, the general practitioner was usually a "singlehanded, professionally isolated, private entrepreneur." The more isolated the institution the greater the tenacity of custom and tradition, and Professor Titmuss suggests that his past isolation is partly the cause of the general practitioner's difficulty in adjusting himself easily to the swift technical changes in medicine and in accepting the necessity for greater reliance on the help of his colleagues.

Divided skills have unfortunately, but perhaps not unnaturally, brought divided loyalties, and Professor Titmuss would admit that these have been accentuated by the N.H.S., which has tended to centre the consultant services on the hospitals and to deprive the general practitioner of his place as the ultimate source of consultant practice. But if some aspects of the N.H.S. and of specialisation have tended to divide the profession and medicine, by fostering group practice and teamwork they are also potentially cohesive influences. Science has already offered the general practitioner effective new drugs, such as the antibiotics, which he can use in his own practice. The National Health Service has not only offered his patients care in hospital: it has also promoted the domiciliary services with whose help he can treat more of his patients in their homes. His growing preoccupation with early mental disease offers him new scope in preventive medicine. But these changes, though offering him new opportunities and more effective means of treatment, have destroyed some of his reliance on his personal interpretation of clinical experience, just as the growing knowledge and expectations of his patients have deprived him of some of his traditional unquestioned authority.

The National Health Service by providing an official whipping-boy has enfranchised complaints—from doctors and patients alike. But, as Professor Titmuss points out, many of these complaints are also made against private practice in the United States. In his view the true target is the changes in practice and the shifts in emphasis caused by "the eruption of science into medicine." The National Health Service is not responsible for these changes, and indeed in many ways is helping medical practice to assimilate them by providing a framework "through which medicine may more nearly fulfil its honoured purpose, the means by which the freedom of doctor and patient alike may be enlarged."

CORTISONE AND RECURRENT POLYNEUROPATHY

THERE is suggestive but not conclusive clinical evidence that in acute infective polyneuropathy of Guillain-Barre type cortisone may stop the rapid deterioration and may hasten recovery once deterioration has been stopped.[1 2] Austin,[3] of the University of Oregon, has described a remarkable case of recurrent polyneuropathy which indicates clearly that corticotrophin and cortisone were of value in treatment. A number of cases of recurrent polyneuropathy of unknown ætiology have been recorded since the first description by Targowla in 1894.[4] Typically the patient is a young adult who over many weeks or months develops a symmetrical, chiefly motor and distal, polyneuropathy, possibly with cranial-nerve involvement and an increased content of protein in the cerebrospinal fluid. Disability is greatest after four to five months, and the patient then begins to improve slowly and often recovers completely. After months or years of normal health a second attack occurs. In the 32 recorded cases reviewed by Austin the average number of attacks was three, and 4 patients died during an attack.

Austin's patient was a man, aged 40, who in five years had twenty attacks of polyneuropathy, and extensive investigation did not reveal the cause. The first attack became steadily worse for eight months, intramuscular corticotrophin halted the progress of the disease, this was followed by intravenous corticotrophin, improvement started within three days, and in two months he was without symptoms and was back at work. After being well for eleven months he had a similar attack with slow deterioration, and after three months he was severely disabled. Deterioration continued when he was given intravenous infusions of glucose and water as a placebo, but improvement started on the fourth day on which he was given an intravenous infusion containing corticotrophin. Studying this patient's recurrent attacks over five years, Austin found that there was a consistent, reproducible, and predictable pattern of response to corticotrophin, cortisone, prednisone, and placebos. Improvement began after the hormones were first given or the dosage was increased, bouts began after dosage was reduced, and on each of three occasions significant deterioration occurred during oral, intramuscular, or intravenous administration of placebos. There was a definite time-lag between the start of hormone administration and clinical improvement, this usually varied from five to seven days—a longer lag than in the acute symmetrical polyneuropathies, where two to three days is usual.

In this unique case the value of hormone treatment is clear, but, as Austin says, the hormones temporarily suppress clinical manifestations when the neuropathy is

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1 Graveson, J S *Lancet*, 1957, i, 340

2 Jackson, R H., Miller, H., Shapira, K. *Brit. med J* 1957, i, 480

3 Austin, J H *Brain*, 1958, 81, 157

4 Targowla, J *Rev neurol* 1894, 2, 465

active but do not cure the disease, and the patient now appears to be having continuous hormone treatment The mechanism by which cortisone acts in this case is by no means clear In 11 of the 32 reported cases of recurrent polyneuropathy that are reviewed, clinical enlargement of peripheral nerves was recorded In this patient's first two episodes, when there was a delay of three months or more before hormones were administered, enlarged firm nerves were felt, but in the later bouts, when hormones were given in the early stages, there was no clinical enlargement Biopsy of the left sural nerve in the second bout three weeks after corticotrophin had been started showed mild to moderate interstitial and subperineural œdema Austin does not consider that the dysfunction in the peripheral neurones was due to a compressive effect of this interstitial œdema, and he suggests that the œdema is due to distended capillary and cell-membrane permeability and that this might seriously affect fluid-electrolyte distribution and other metabolic functions of the axone-myelin-Schwann cell complex with resulting impairment of function

ESCHERICHIA COLI IN FARM ANIMALS

Escherichia coli was long suspected in an indeterminate way of causing diarrhœal diseases in man and animals, but conviction had to await the work of Kauffmann in subdividing this universal species into types or subspecies by serological methods It is now well known that some of these types may be associated with acute diarrhœa in infants both the clinical picture and the pathological changes in bowel and kidneys are fairly characteristic The evidence that these types are the " cause " (in the sense that *Salmonella typhi* is the cause of enteric fever) is suggestive The organism is present in the bowel at the acute stage of the disease in almost pure culture, and it disappears in convalescence The disease produces specific antibodies in the blood and has been reproduced experimentally In certain children's hospitals the disease has behaved as an extremely infectious specific fever, and methods of control based on this thesis have had some moderate success The pathogenic types of *Esch coli* have, however, been found quite frequently not only in adults but in healthy infants congregated in institutions An epidemic is due to a single type, but within an institution this type may for no obvious reason disappear or be replaced by another type Some types (e g, 0 111 B 4) which did most damage ten years ago are nowadays almost extinct

Certain serological types of *Esch coli* have been identified as the cause of scours in calves, and, as in man, the types responsible have changed over a period of years (With one or two exceptions the types pathogenic to calves have so far been harmless to infants) Because calves can be observed experimentally, we know rather more about the epidemiology of their disease [1] than that in babies Maternal antibodies transmitted in the colostrum normally give a high degree of protection, but if the calf is brought into contact with pathogenic types of *Esch coli* antibodies to which are not present in the colostrum it will probably die This is borne out in practice by the experience that it is unwise to move a calf to a fresh environment in the first few days of life or even to move the cow shortly before the calf is born The protection given by colostral antibodies is not absolute an overwhelming infection by a virulent type will sometimes swamp the defences

" Gut œdema " has been known for many years as a serious disease of pigs, and is usually ascribed to dietary indiscretion The name is apt, but the œdema may affect other parts postmortem appearances are not unlike those in some cases of " coli enteritis " in infants New light has been thrown on the ætiology of this disease by the observation that in almost every case *Esch coli* of one of four specific serological types are present in the bowel and mesenteric glands, and that the disease can be reproduced by the intravenous injection of an extract of one of these types [2] There is also some evidence that a specific antiserum may benefit some infected animals Of the epidemiology of this disease we are still rather ignorant Most commonly it attacks store pigs of 10–14 weeks but it may occur in younger animals It does not seem to have the characters of an acutely infectious fever, but traditionally its onset follows a change of housing or of diet To confuse the inquiring veterinarian there arises in young piglets an apparently distinct diarrhœal disease which seems to be akin to scours in calves, the types of *Esch coli* responsible for this are distinct from those associated with gut œdema

These diseases of man and animals have many likenesses but also some obvious differences In each case there are reasonable grounds for believing that the observed pathological changes are due to toxins produced by specific types of *Esch coli* (Although one or two of the types causing scours have been found in infants it is generally true that each disease is associated with its peculiar specific types) It also seems clear that the types which cause infantile enteritis and scours are not invariably pathogenic In this connection Lovell has suggested that the soil is as important as the seed, and by his own work has demonstrated the importance of immunity acquired from the mother Babies, of course, get their maternal antibodies through the placenta, and there is no evidence, so far as we know, that these play any part in protecting the infant against enteritis due to *Esch coli* A change of environment (which means, probably, contact with alien types of *Esch coli*) seems to be of real importance in precipitating these diseases among animals Its danger in man is less easy to establish Because we live in relatively isolated families, diarrhœal diseases of infants are likely to be seen in epidemic form mainly in institutions, but, in fact, single infections in the home and in the communal nursery are not uncommon

There is one other factor which tangles further an unruly skein Beyond much doubt there are diarrhœal diseases of man and animals due to filterable agents [3,4] In man these are highly infectious but less severe than those due to *Esch coli* On the analogy of hog cholera, a viral disease almost always complicated by infection with *Salmonella choleræ-suis*, the suggestion has been made that all these enteric diseases of young animals are primarily due to infection with one or more viruses but are complicated and perhaps made more severe by the specific types of *Esch coli*

These diseases are receiving much attention, and on economic grounds alone they deserve it Our knowledge of the comparative morbid anatomy is scanty Observations in the field and the hospital have been often disjointed and unplanned The methods of experimental epidemiology which have been so fruitful in the calf can be applied to pigs and even, in part, to man

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[1] Lovell R *Vet Rec Annotations*, 1955, 1, 1

[2] Sojka W J, Erskine R G, Lloyd, M K *Vet Rec* 1957 69 293

[3] Brandly, C A, McClurkin A W *Ann N Y Acad Sci* 1956, 66, 181

[4] Hodes, H L *ibid* p 215

Special Articles

MINAMATA DISEASE

AN UNUSUAL NEUROLOGICAL DISORDER CAUSED BY CONTAMINATED FISH

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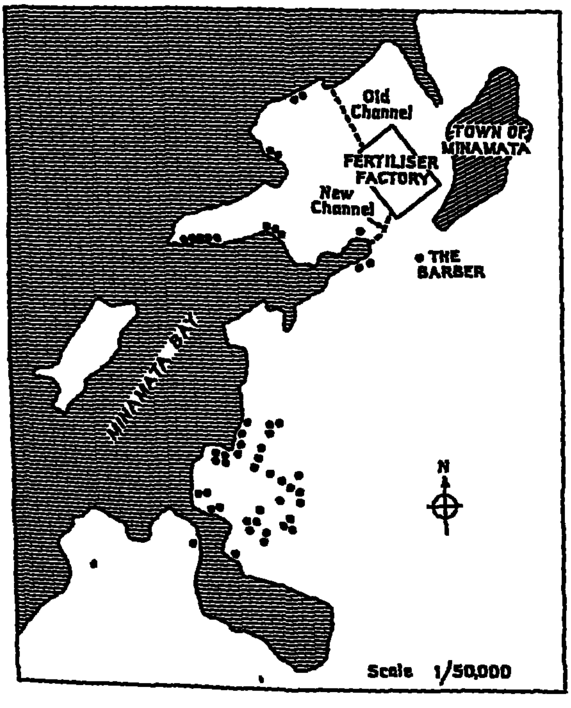
Minamata is a small industrial town near the south-west coast of Kyushu, the most southerly of the main Japanese islands The chief industry is provided by a large artificial-fertiliser factory, the effluent from which empties into Minamata Bay A number of villages are located on or near this bay, mainly to the north and the south. The short coastline opposite the middle of the bay is uninhabited (see figure)

From the end of 1953 a mysterious nervous illness began to affect the villagers near the bay, and by 1956 it had assumed epidemic proportions The outbreak was investigated by a number of departments of Kumamoto University and the results were published last year in the *Kumamoto Medical Journal* (Kitamura et al 1957)

Clinical Features

During 1956, 15 cases (9 adults and 6 children) were admitted to Kumamoto University Hospital

The onset of illness was acute or subacute and usually unattended by fever or constitutional symptoms In all the adults numbness developed in the extremities and sometimes around the mouth, often accompanied or followed by slurred speech, unsteady gait, and increasing disability Most of the patients complained of deafness and disturbance of vision, the latter being associated with generalised constriction of the fields Dysphagia and increased salivation were less commonly observed Insomnia was a striking feature in 3 adults and 2 children 6 adults showed emotional lability in the form of euphoria or depression The seriously ill patients were mentally confused, drowsiness and stupor alternated with periods of restlessness and shouting Cerebellar ataxia and dysarthria were always present, but nystagmus was noted in only 1 patient Choreiform or athetotic movements were observed in several adults, and hemiballismus in 1 The deep reflexes were exaggerated in 4 patients and depressed in 2, an extensor plantar response was noted twice Distal hypæsthesia was found in the limbs of 3 adults, but in reports no mention was made of vibration or postural senses Epileptiform attacks occurred in 1 child and 1 adult during the period of observation.



Based on a map published by the public-health department of Kumamoto University to illustrate the distribution of 52 cases of Minamata disease

4 adults showed a mild degree of secondary anæmia The cerebrospinal fluid was normal except for a moderate pleocytosis in 1 patient The serum showed an increase of gamma-globulin. An abnormal amount of aminoacids was found in the urine of the more seriously ill adult patients Estimation of serum-copper was normal, manganese was found in excess in 1 case

The course of the disease fluctuated and its results were variable, the most severely affected died, while others remained incapacitated in varying degree. Improvement in hospital was occasionally followed by relapse on returning home

Pathology

The brain and certain internal organs from 4 patients, and one spinal cord, were available for study

Apart from small areas of necrosis in the intestinal mucous membrane, and scattered areas of necrosis in the liver in 1 case, there was no abnormality of the viscera The main findings in the central nervous system were (1) cell degeneration, which was most marked in the granular layer of the cerebellum, while changes of varying degree were apparent in the basal ganglia, hypothalamus, midbrain, and cortex, (2) dilatation of the perivascular spaces, with occasional softening, but no true demyelination, (3) œdema and occasional small hæmorrhages, and (4) reactive gliosis The spinal cord showed minor changes, the anterior-horn cells were unaffected

Epidemiology

The public-health department of Kumamoto University reported 52 patients, all of whom frequently ate fish from Minamata Bay There were 39 cases in four villages with a total population of 2091, giving a morbidity-rate of 19 per 1000 population The remaining 13 were scattered over seven districts with a population of 7988, giving an overall rate of about 5 per 1000

The figure shows that with one exception, namely a barber living on the outskirts of Minamata Town who fished in his spare time, all the cases occurred in the neighbourhood of the bay The patients were distributed among 40 families In 36 (90%) of these at least one member fished in the bay, but in 48 (71%) of 68 neighbouring families who were unaffected no-one fished. 25 of the 40 affected families every day ate fish or shellfish which came from the bay, and the remaining 15 consumed fish from the bay two or three times a week. By contrast, only 5 of the 68 unaffected families were in the habit of eating fish daily from the bay, and most of them ate less fish per week than the affected families Of 31 males and 21 females who became ill, 10 were children under the age of ten, but no infants were affected By December, 1956, a further 4 cases had been reported. Of the original 52 patients, only 3 were able to return to work within 6 months, 9 improved, and 23 were stationary, there were 17 deaths This gave a case-mortality of 33% 8 patients died within 2 months and 4 within a year

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Fishing in Minamata Bay was mainly carried out at night; on returning home in the morning the fishermen and their families usually ate raw the freshly caught fish. But the survey of the public-health department showed that cooked as well as raw fish can cause the disease, which suggests that the toxic substance is thermostable. Those who ate fish for breakfast seemed likely to consume more daily than the schoolchildren who left home before the morning catch had been brought in; this may account for the escape of several children of families in which other members were affected.

A Disease in Animals

A disease also appeared in animals which had eaten fish or shellfish.

In the 40 affected families there were 61 cats and 50 died between 1953 and 1956, sometimes in as little as 2 days. Unsteadiness, frequent falls, circling movements, and convulsions were observed; forced running appears to have caused some of them to enter the sea and be drowned. The 68 unaffected families owned 60 cats and of these 24 died. 5 pigs and 1 dog died, also many crows which were in the habit of settling on a floating landing-stage where the returning fishermen tied up. The brains of 10 cats were examined; the changes were similar to those observed in the human material, the granular layer of the cerebellum being especially affected. The disease could be readily produced experimentally in cats by feeding them for 2 to 4 weeks with fish from Minamata Bay.

Chemical Investigations

The chemical investigations were difficult to evaluate since several departments carried out independent analyses of human and cat material, and of fish from the bay, with varying results, but the following appear relevant.

(1) Some fish and shellfish from the bay showed increased amounts of manganese, selenium, and copper as compared with controls from another area, while the amounts of thallium, arsenic, lead, and iron were not significantly raised.

(2) The silt from that part of the bay into which the effluent from the fertiliser factory flowed was dark in colour, mudlike in consistence, and contained sulphur and a toxic sulphur derivative, mercaptan (ethane-thiol). Large amounts of selenium, and smaller amounts of manganese, thallium, copper, lead, and iron were also found in the silt, all were increased as compared with the analysis of sand from another part of the coast.

(3) Selenium was present in human and cat livers in roughly the same proportion as reported in cases of selenium intoxication, and manganese was found in the hair of the affected cats.

(4) The raw material used by the factory contained, inter alia, thallium and selenium.

(5) In 1953 the principal products of the factory were ammonium sulphate, ammonium and calcium phosphate, sulphuric acid, carbide, and nylon.

It was concluded that the outbreak had been caused by a toxic factor in fish but there was no agreement as to its nature.

Personal Observations

During two visits to Minamata in February and March, 1958, we had the opportunity of examining 16 patients in their homes, and 6 others in Kumamoto University Hospital.

Multiple cases occurred in 3 families.

Egoshita family.—During 1956 both parents and 2 sons (aged eleven and nine) noticed mild peripheral numbness, dysarthria, and ataxia, but they all gradually recovered over a period of several months; a daughter (aged five) developed dysphagia in addition, and died in hospital of aspiration pneumonia. 1 other older son living at home was not affected.

Kaneko family.—The father became ill with dysarthria, tremor, and ataxia during 1954; his condition slowly deteriorated and he died in June, 1955. Also during 1954, the elder son (aged five) developed similar symptoms associated with spastic weakness of the left leg, but he gradually improved after a few months. The younger son had a severe attack of measles in 1956, when eight months old, and afterwards failed to sit up, talk, or walk. But he was entirely breast-fed until after the age of two—which makes the diagnosis of Minamata disease unlikely, since the mother remained well throughout.

Tanaka family.—In March, 1956, a child of six was febrile for 1 day, and during the next 2 or 3 weeks developed progressive ataxia, dysarthria, dysphagia, and visual deterioration. In April she became agitated and had a generalised convulsion; nasal feeding was necessary and she was admitted to hospital. In February, 1958, she was mute, deaf, and apparently mentally defective. She could not sit up though she was able to see large objects. The pupils and fundi were normal; all four limbs were flexed and spastic. A younger sister (aged three) developed progressive dysarthria and ataxia in April, 1956, and later dysphagia and incontinence. When seen by us she was mute and unable to sit up, though she could move all her limbs freely. The optic discs were normal, the deep reflexes were exaggerated, and the plantar responses equivocal. The mother was normal, but no details are available of the rest of the family. (The history of these 2 sisters was taken from notes published in the *Kumamoto Medical Journal*—pædiatric department, cases 1 and 6—in 1957.)

Discussion

The salient facts regarding this unusual outbreak seem reasonably clear. In a scattered community, living near the sea, there appeared an obscure neurological illness which assumed epidemic proportions within 2 years, causing death in more than a third of its victims and serious disability in most of those who survived. Concurrently, a fatal illness affected domestic animals and also scavenging crows and fish in a nearby bay. Two facts were established—firstly, that there existed a close relationship between the eating of fish and the occurrence of the disease, and, secondly, that the fish responsible for the outbreak had been caught in Minamata Bay. This last observation was supported by the results of a ban placed on fishing in the bay which came into operation in November, 1956, since when no fresh case has been reported. Chemical analysis of silt from the bay suggested that the water was polluted by effluent from a fertiliser factory. Inquiry showed that the factory introduced no new process in 3 years before the outbreak. Professor Kitamura, however, pointed out that until 1950 the effluent was diverted into the open sea by a channel to the north of the factory, but in 1950 this was closed and a new one constructed which runs directly to Minamata Bay (see figure).

Clinically, the subacute onset of numbness in the distal portion of the limbs and occasionally around the mouth suggested peripheral nerve involvement. In a few patients the numbness became generalised and was accompanied by sensory ataxia, recalling the so-called "sensory neuropathy", in which posterior-root ganglia are primarily affected, usually as a complication of carcinoma (Denny-Brown 1948, Henson, Russell, and Wilkinson 1954). Cerebellar symptoms were conspicuous at the onset but nystagmus was a rare finding. Not infrequently there was deafness and disturbance of vision; in the few cases in which perimetry was performed the visual fields were generally constricted. With one exception, the optic discs were normal in patients examined 2 or 3 years after the onset. Pyramidal signs were occasionally found. In the more seriously ill patients there were symptoms of an encephalopathy—i e , mental confusion, stupor or coma (in the fatal cases), convulsions, involuntary movements of varying type, and insomnia In some, the presence of intellectual deterioration, mutism, epilepsy of late onset, an increasing degree of limb spasticity, and incontinence suggested a form of progressive neuronal degeneration Involuntary movements were occasionally prominent in the early stages, but we did not observe parkinsonism or choreoathetosis as a sequel, though, in one case, there was a striking tremor of the red nucleus type

There seems to be a fair measure of agreement between the clinical and pathological findings as to the anatomical localisation of the disease, but the ætiological factor is uncertain. In the published reports on Minamata disease no mention is made of gastrointestinal symptoms, but the possibility that a toxic metallic compound was responsible for the outbreak is supported by the occasional complaint of increased salivation and by the finding of areas of intestinal necrosis in each of the 4 patients who came to necropsy

Some of the neurological features of Minamata disease have been observed in toxic states due to certain metals

Methyl mercury compounds may cause ataxia, dysarthria, constriction of the visual fields, an occasional extensor plantar response, and, experimentally, peripheral neuritis and degeneration in the granular layer of the cerebellum (Hunter, Bomford, and Russell 1940) Thallium may cause a complex neurological picture—i e , psychosis, choreiform movements, inversion of sleep rhythm, deafness, retrobulbar neuritis with optic atrophy, ocular pareses, bulbar palsy, pyramidal signs, and peripheral neuritis In severe cases convulsions may be followed by coma and death (Prick, Smitt, and Muller 1955) In carbon-disulphide intoxication manic-depressive psychosis and mental confusion may be prominent, while peripheral neuritis, disturbance of vision, optic atrophy, deafness, and, in the chronic stage, parkinsonism may occur Manganese mainly affects the basal ganglia, resulting in a variety of striatal symptoms, including parkinsonism. Mild psychiatric symptoms have been attributed to chronic intoxication with selenium (Lemley and Merryman 1941), but we have been unable to find reference to neurological manifestations

Degeneration in the granular layer of the cerebellum, a conspicuous feature of Minamata disease, is non-specific, having been found in various pathological conditions such as anoxia, hyperglycæmia, hypoglycæmia, mercury intoxication (bichloride and methyl compounds), and chronic alcoholism (Leigh and Meyer 1949, Neuberger 1957)

Of the three metals manganese, selenium, and thallium, which have received most attention from those investigating the disease, only the last-named seems likely to produce on the nervous system an effect similar to Minamata disease It is hoped that the results of work which continues in Kumamoto University may throw light on the nature of the toxic agent responsible for this unusual outbreak.

Summary

The clinical, pathological, and epidemiological features are described of an unusual neurological illness which, between 1953 and 1956, attacked villagers living near Minamata Bay in Kyushu Island, Japan

Characteristically the disease affects the peripheral nervous system, the cerebellum, hearing and vision, and less frequently the pyramidal tracts In severe cases an encephalopathy may be followed by signs suggesting progressive brain damage

The pathological findings are widespread neuronal degeneration, particularly in the granular layer of the cerebellum, and areas of intestinal necrosis

Fishermen and their families were mainly affected and the evidence suggests that the disease was caused by eating fish caught in Minamata Bay

Concurrently a disease associated with ataxia and convulsions proved fatal among domestic animals, especially those belonging to affected families, and also among scavenging crows

Although the cause is not yet established, the evidence so far points to the toxic action of an inorganic chemical compound contained in the effluent which flowed into Minamata Bay from a nearby fertiliser factory

We would like to acknowledge grants received from the National Institute for Neurological Diseases and Blindness Bethesda 14, Maryland, and to thank Prof R Miyagawa who afforded us facilities for this study.

REFERENCES

Denny-Brown, D (1945) *J Neurol Psychiat* 2, 73
Henson, R. A , Russell, D S , Wilkinson, M (1954) *Brain*, 11, 82
Hunter, D , Bomford, R. R., Russell, D S (1940) *Quart J Med* 33, 193
Kitamura, S , Katsuki, S , Kawamei, Y , Tokuomi, H., Nagano, S , Osaki, M , Seben, E., Takeuchi, T , Rokutanda, G , Irukayama, K., Sera, K.* (1957) *Kumamoto med J* (Suppl , January and June)
Leigh, A D , Meyer, A (1949) *J Neurol Psychiat* 12, 257
Lemley, R. E., Merryman, M P (1941) *Journal Lancet*, 61, 435
Neuberger, K. T (1957) *Arch. Path (Lab Med)*, 63 1
Prick, J J G , Smitt, W G S , Muller, L (1955) Thallium Poisoning Amsterdam

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* Owing to the large number of authors only the names of principals are given

U F A W

(The Universities Federation for Animal Welfare)

THE medical profession exists for a purpose which is essentially humanitarian, and the humane mentality which belongs to it may be expected to extend beyond the human species to the other animals, which are, so to speak, man's poor relations But the practical expression of this interspecific sympathy, which is a logical development of man's intraspecific social conscience, has been hindered during the past three-quarters of a century by the controversy about vivisection, and in lesser degree by other propaganda inspired by a love of animals but conducted in an over-emotional way which is repugnant to the scientific mind

There is, however, one animal-welfare society which provides a channel through which medical men can safely give effect to their sympathy for animals without compromising their intellectual integrity The policy of UFAW is determined by a board of directors who are elected by the ordinary members, and these are required to have a university or professional qualification Although a university education is not an infallible guarantee of soundness of judgment, this arrangement has in practice proved a sufficient safeguard against the influence of extremists Moreover UFAW has found it necessary to rely largely on veterinarians and zoologists for practical guidance, thus ensuring a sound factual basis for its policies

Its president is Dr Edward Hindle, F R.S , sometime regius professor of zoology at Glasgow, its scientific advisory committee is composed largely of research scientists, under the chairmanship of Prof P B Medawar, F R.S , the president of its veterinary section is Prof W I B Beveridge, of the Cambridge Veterinary School, its technical secretary is a medical woman, Miss Jean Vinter, M D , and its founder and secretary-general, Major C W. Hume, is a physicist with an amateur interest in biology.

LABORATORY ANIMALS

Most of the other animal-welfare societies in the British Isles are committed to an antivivisectionist policy, though two or three leave the subject entirely alone UFAW is the only one which has developed a positive and constructive policy in this connection

The UFAW Handbook on the Care and Management of Laboratory Animals, now recognised as the standard textbook on its subject, was first published in 1947, and, in conjunction with the Laboratory Animals Bureau (now Centre) of the Medical Research Council and the Animal Technicians Association, has been responsible during the past decade for a vast improvement in the comfort as well as the usefulness of laboratory animals

The editor of the first edition was A N Worden, some time Milford professor of animal health at Aberystwyth and, in his student days, chairman of the students' committee of UFAW The second edition, edited jointly by A N Worden and Dr W Lane-Petter and recently published, had to be so much enlarged that the original publishers were unwilling to publish it, although, at the same time, they were unwilling to relinquish the copyright UFAW therefore had to buy the latter for a sum which will entail a financial loss on the whole transaction, but the object has been to provide information rather than to make a commercial profit

More recently UFAW has turned its attention to laboratory techniques, on which it maintains a research team A symposium last year on Humane Technique in the Laboratory was attended by about 120 research scientists A brief report was published in this journal [1] and most of the papers have been published by the Laboratory Animals Centre as vol 6 of its *Collected Papers* UFAW hopes, in the first place, to see an acceleration of the replacement of animals by unconscious material in tests such as the determination of an L D 50 or an E D 50, which at present entail discomfort For instance, UFAW is sponsoring a research which is being directed by Dr Michael Chance in the medical school at Birmingham and which might, if successful, enable a wide range of such tests to be replaced by one using mice which are anæsthetised and are killed before they recover consciousness A second hope is a reduction in the number of animals needed for a given degree of precision,[2] effected either by statistical techniques, or by genetical homogeneity of response to experimental treatments, or by detection of specific factors which effect variance On the last point, UFAW is sponsoring a research directed again by Dr Chance in Birmingham (The last-mentioned research, incidentally, inaugurates a long-overdue study of the psychology of laboratory animals) A third hope relates to refinement of laboratory techniques for the purpose of reducing or eliminating discomfort As a contribution to this aim a UFAW research fellow, Dr Phyllis Croft, is carrying out electroencephalographic studies of anæsthetics and relaxants in Professor Amoroso's laboratory at the Royal Veterinary College A comprehensive review of the whole problem has been written by Dr W M S Russell, a UFAW Research Fellow, and will be published shortly by Messrs Methuen with the title *The Principles of Humane Laboratory Technique*

WILD AND DOMESTIC ANIMALS

But the laboratory animals are only one, and a comparatively recent one, of UFAW's interests

The gin trap was scathingly condemned for its cruelty by several of those who spoke in defence of research when the Cruelty to Animals Act, 1876, which regulates vivisection, was passed through Parliament in 1876, yet it was finally outlawed no longer ago than July of the present year, as a result of a long campaign An important factor in this success was a four-years' research on the ecology of the wild rabbit which was sponsored by UFAW and for which two M SC degrees were awarded

Again, during a great many years some scores of thousands of unwanted dogs were killed annually by animal-welfare societies by passing electric current between the neck and the hindquarters, and strong opposition was offered, on antivivisectionist grounds, to UFAW's demand for a scientific investigation of the process Eventually it became possible for Dr Phyllis Croft, a UFAW research fellow, to make this investigation, whereupon the British Veterinary Association instituted an independent research which confirmed her finding that, in spite of superficial appearances, excruciating pain was being caused to each animal for about 12 seconds, and that this could be avoided by passing a sufficient current through the brain For this work Dr Croft was awarded the Livesey medal of the Royal College of Veterinary Surgeons

Another research sponsored by UFAW is one relating to humane poisons for wild rats and directed by A N Worden at the Nutritional Research Centre, Huntingdon

Again, at the suggestion of a member of the Home Office Committee on Cruelty to Wild Animals, UFAW called together and administered a committee representing zoologists, sportsmen, and others interested in the otter A research on the ecology of this animal was undertaken with funds contributed mainly by the Nature Conservancy and to a much smaller extent by UFAW, and it is interesting to know that, although this had to be discontinued for lack of funds after two years, within a fortnight of receiving the published report the Prime Minister of Denmark made an order protecting the otter in that country

Some time ago Prof W I B Beveridge called UFAW's attention to the painful disease of foot-rot in sheep, which is very widespread but can be eradicated if certain fully practicable steps are taken With the support of the British Veterinary Association, the British Wool Marketing Board, the National Sheep Breeders' Association, and the National Farmers' Union, UFAW has been conducting an educational campaign on the subject, and is now sponsoring the production of a film which shows technical details of the requisite treatment

THE NEED FOR SUPPORT

UFAW draws its funds partly from the sale of publications (and especially of Christmas cards designed by its honorary artist and chairman, Fougasse) but mainly from voluntary subscriptions and legacies In the latter respect it is at a disadvantage in being precluded from making appeals of the sensational type, which alone open the more lavish purses If it were to become an antivivisection society its financial worries would disappear overnight, but on the other hand its ability to perform its special function would be destroyed It has therefore to rely on subscribers who are both generous and intelligent, and these are not so numerous and wealthy as could be wished

UFAW's primary function is to create or obtain authentic information bearing upon the welfare of animals and to convey this to those who can use it to advantage, including the general public in the case of the less specialised information To this end it is necessary to recruit support among university students, who are the professional men and women of the future, and at present there are branches in ten British universities It is disappointing, however, that there is no organised branch in any of the medical schools, and that the number of qualified medical supporters, though by no means negligible, is small in proportion to the size of the profession

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[1] *Lancet*, 1957, i 1035

[2] Hume, C W *ibid* 1957, ii, 1049

Information relating to the work of UFAW, including a list of publications, may be obtained from the Federation at 7A, Lamb's Conduit Passage, Red Lion Square, London, W C 1

The Wider World

GALEN IN CHINA

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IN December, 1955, I visited China and saw something of the costly, strong, official drive to boost traditional remedies and practice Nothing in the medical scene impressed me more, and like Fox[1] I came away feeling that political rather than scientific motives lie behind it Under Communism, of course, all activities are supposed to contribute to the construction of the socialist State, and to this extent every movement in a 'Communist country is bound to demonstrate, or at least pretend, a political element. Yet it is none the less disturbing to find a naturally non-political field like that of therapeutics the subject of a determined political assault. Men trained in Western medicine are being forced to accept and adopt ancient magics

One medical official I met early in my trip said that traditional practitioners were being given elementary instruction in health rules, and were being taught to undertake certain tasks such as vaccinations and simple treatments He pointed out that there is still a grave shortage of Western-trained doctors, that the traditional practitioner is the village doctor of China, the man the people know and trust, and that therefore traditional doctors are being employed for certain urgent and widescale medical activities I was left with the impression that these men are being put to good use until they can be replaced by the products of the medical schools Since China has some 600 million people, about half-a-million traditional practitioners, and only some 70,000 doctors trained in Western methods, this seemed a wise course

But I found later that the accent was not upon using the traditional doctor as a medical auxiliary, not upon encouraging the old to accept the new, but upon forcing acceptance, approval, and admiration of the whole established rigmarole of native therapy In an article entitled "Why Our Western-Trained Doctors Should Learn Traditional Chinese Medicine", Dr Fu Lien-Chang[2] president of the Chinese Medical Association, wrote

> "How many western-trained doctors since Liberation have studied Chinese medicine and have obtained successful results? Very few indeed! The great majority of western-trained doctors have never considered the learning of traditional medicine as a task that should be undertaken seriously The responsibility for this state of affairs lies with the health administration and the Chinese Medical Association for not having carried out their task of leadership
>
> "Take myself for example Although I have attended patients with practitioners of our native medicine, I have never considered Chinese medicine as a subject I should learn I have never seriously studied any books on traditional medicine Hence, even today, I remain a complete ignoramus as far as our native medicine is concerned. As a leader in our country's health work and as Head of the Chinese Medical Association, I am ashamed to confess this I must seriously take up the study of Chinese medicine."

And later

> "In the past we have organised training courses for old-time physicians to learn western medicine. This, although necessary, is *not of the greatest importance* The Central Committee of the Party and Chairman Mao have enjoined us that the key to the problem is that our western-trained doctors should study traditional Chinese medicine It must be emphatically stated that not only should doctors of traditional medicine learn western medicine but, particularly, western-trained doctors should study Chinese medicine"

Dr Fu leaves no doubt about the direction of the effort demanded Nor is doubt left after visits, in Peking, to the Institute for Research into Herbal Medicine and the Institute for Research into Acupuncture.

THE INSTITUTES

These institutes are ill named They are not research laboratories, but propaganda bureaus

Acupuncture

The Acupuncture Institute, housed in a former Buddhist monastery, devotes the better part of its space to an exhibition.

The public come daily in organised groups The tour, conducted by a hard-talking guide, takes nearly an hour A brief account of three of the exhibits will show the tone of the place

> A placard states that "This summer one acupuncture doctor cured 250 patients at a total cost of $12.50 By orthodox treatment, 35 similar patients would cost $339 50 to cure On an average, each case took 1 12 days By Western methods, each would have taken 3.5 days"
>
> A map of the world has a gleaming acupuncture needle overlying China From this needle radiate ribands to all the other countries which have accepted and adopted acupuncture—among which England, Canada, and the United States are included
>
> A show case holds envelopes addressed to the institute and bearing a variety of foreign stamps They are evidence of the unsolicited testimonials which arrive daily from all quarters of the globe.

These are fair samples from a large collection of manuscripts, photographs, impedimenta, and charts, all designed to convince the layman that acupuncture is and always has been a very good *thing, and that Western medicine comes a poor* second

Graphs and histograms abound. There are X-ray photographs Statistics are worked to two decimal figures The grubby old magic is given a fine, new, white laboratory gown.

As well as the exhibition, the institute houses "research departments" (one department, one room) of physiology, biochemistry, metabolism, pathology, bacteriology, and statistics (I am not quite sure of this last title, but it was the best I could make of the description given to me) When I was there, "research" was not yet fully under way, but the purpose of the "research departments" was clearly that of providing "scientific proof" for acupuncture's claims

Finally, and perhaps most importantly, the institute is a training school Doctors already trained in Western medicine are given an intensive course so that they may go back to the medical schools as teachers

Herbal Medicine

At the Institute for Research into Herbal Medicine, a more sober tone prevails The native practitioner who dispenses the remedies of the Chinese pharmacopoeia is very like his Western counterpart of a hundred and fifty years ago The pretence to equality with Western medicine is therefore more easily sustained, and there is not so much need for vigorous demonstration of superiority and "scientific worth"

The institute is run like any Western clinic. There are consulting-rooms and there are laboratories and there are lecture rooms, and the traditional doctors on the staff wear long white coats and carry stethoscopes round their necks There is also the inevitable exhibition. But, again, the accent is not upon inquiry into those remedies which appear to have some pharmacological activity, it is not upon making a critical effort to harvest what is good and reject what is useless, it is upon presenting and sustaining and increasing the influence of the whole tradition as it is and has for ages been.

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[1] Fox T F *Lancet* 1957, ii 935
[2] Fu Lien-Chang *Chin. med J* 1955, 73, 363 This article also appeared at the front of eight other professional journals

It is hard to imagine how the methods of science could usefully be applied to acupuncture, but in the field of herbal medicine there is obvious ground for fruitful research Chen and Schmidt's work on ephedrine is the classical example of what may be achieved It is therefore disappointing to find that such work is not a major effort within the central temple of herbal medicine, and to be told, in answer to a question, that " Chemical analysis is also undertaken, but is not the main aim of research, because from some of the herbs it is not possible to extract the active principle " The belief is encouraged that the art is being boosted for purposes other than its possible contribution to a system of rational therapy

True enough, work of the Chen-Schmidt type is going on in China, but such efforts are largely made not at the centres of herbal medicine but in the medical schools and hospitals where Western doctors are being so vigorously urged to " cooperate " and show a lively interest in their traditional heritage

THE FUTURE

My host at the Institute of Herbal Medicine told me of future plans

Doctors will get their training in Chinese medicine whilst undergraduates in the medical schools No new purely traditional doctors will be produced The modern and the traditional modes will be taught side by side, so that after a period there will no longer be two groups of doctors in China, but a single group composed of men trained in the new synthetic lore There will not be texts on traditional medicine and other texts on Western medicine, but new books will be written to combine the teachings of the two disciplines There will not be teachers of the old and others to teach the new, instead each teacher will preach the double gospel, not as separate subjects, but as one This is for herbal medicine Acupuncture, which is a " specialty ", will have its own share of the curriculum, amounting to some 160 hours

However, the full synthetic course will not operate until after the end of the third Five Year Plan, and that time lies ten years from now

A more recent assessment of the situation was given last year by Ho Piao[3], vice-minister at the Ministry of Health Reviewing the development of hygiene and health work under the first Five Year Plan, he wrote

> " During the past few years great efforts have been made in developing traditional medicine In China there are now more than 500,000 traditional practitioners with over 40,000 apprentices Four colleges for the teaching of traditional Chinese medicine have been opened together with six schools and twenty-three centres for refresher courses In addition there are 144 hospitals and 453 clinics where traditional Chinese medicine is practised exclusively Over 20,000 traditional doctors have joined the government health service At present 5,000 highly trained modern doctors are studying traditional medicine, among whom 300 are devoting their full time to it An institute for research into traditional medicine has been established All colleges of medicine and pharmacy pay particular attention to research into traditional Chinese medicine and pharmacy "

This statement hardly suggests that the pure herbalist is on the way out, on the contrary it shows that earlier plans for boosting traditional medicine are being vigorously pursued So far as " cooperation " between the old and the new is concerned, the picture seems wholly one-sided " 5,000 modern doctors are studying traditional medicine " (despite the crying need for their efforts in other tasks) There is no mention of traditional doctors being trained in Western ideas

A marriage having been ordained, one unwilling partner is being steadily forced by determined in-laws toward an unhappy consummation How will the children turn out ?

INCOMPATIBLES

There is no strict proof that the ultimate will of God is expressed in the being of the Royal College of Physicians of London (however some of the Fellows may feel), and, on the other side, there is no doubt that the herbal doctor in China provides, and has for centuries provided, services sorely needed by a sick man and his relatives The choice between modern and traditional medicine is not, therefore, a choice between the ideally good and the wholly bad Nevertheless an equally absolute difference does divide the two One is science and the other is not

Herbal medicine is a mixture of empiricism and superstition acupuncture is unspoiled magic The whole nature of contemporary Western medical thought and practice rests upon the rules of science It is therefore logically impossible to teach the two systems effectively side by side, for a man who believes in the one cannot appreciate the other It must follow that a man cannot teach or learn or practise both together unless he avoids thinking about either

The whole medical effort must be reduced to the faithful practice of decrees Doctors must recognise the Party as the only competent authority in medicine, as in all else And first among the results to be expected is that advance will cease *Medicine in China must look forward to* a period of inanition exactly parallel to that which seized medicine in Europe for centuries under the grip of the galenical philosophy The only advances permitted will be those introduced from outside after careful vetting and approval by the State

Is this what is required and foreseen ?

AN EXPLANATION

I have two reasons for suggesting that the Chinese Government does want and expect the results I have imagined Firstly it is an accepted working rule of historians that an intelligent man foresees the logical consequences of his deeds, and there is certainly no doubt that the present leaders of China are highly intelligent Secondly, it is significant that the full synthetic training is not to be introduced for another ten years Mao Tse-Tung pronounced the need for cooperation between modern and traditional doctors in October, 1944 Admittedly, the training of teachers and the writing of texts must precede remodelling of the medical course, but by Communist standards, twenty-four years is a strangely long preparatory period, and out of keeping with what we know of their usual rate of progress towards a decided end However, if the leaders realise how their programme must alter the whole nature of medical thought and practice in China, then another reason for delay emerges

The present structure of medical services and medical training must depend largely upon the work and enthusiasm of doctors and medical scientists who have had their training in Western schools, either inside or outside China, many of the best of whom will have spent some time abroad in postgraduate training and practice It is essential to retain the effective services of these men until they can be replaced by more amenable domestic products It would be impossible to bring about their genuine conversion to the ancient faiths The Government is showing its wisdom in not risking shipwreck by forcing too sharp a change of course

Then, if the consequences are foreseen, what is the motive ? It is certainly nothing trivial like a misguided chauvinism, or an undue influence by vested interests in high places The effort is far too large, the results too grave, to allow belief in such answers Is the movement inspired by a deep governmental faith in the "scientific" virtues of traditional medicine? That would be a curious judgment from a group of hardheaded dialectical materialists Is it simply an attempt to make the native cures seem good to the people in view of the fact that for many years to come no other sort of medical care will be available to most of China's millions? This would be a satisfying answer if the main effort was in public propaganda supporting herbalism It is no explanation for the changes being forced upon Western practice

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[3] Ho Piao *ibid* 75, 953

Possibly there is no one answer, and possibly some or all of the factors just considered helped to shape policy, but I suggest that a prime and purely political motive lies behind all

The doctor, unlike the chemist or the physicist or the engineer, is necessarily always in close contact with the people of the community he serves, and if he is any good at all he has a large, personal, and direct influence on his patients and on his patients' friends and relations I suggest that a man trained in the critical and almost iconoclastic school of contemporary Western medicine is not a suitable person to wield moral and intellectual authority among the citizens of a Communist State If he himself is a dedicated believer in Marx-Leninism, he may achieve a sort of working schizophrenia, having a mystical faith in the gods of State, whilst keeping a fairly effective spirit of independence and inquiry alive within the half of his mind that he uses for his job When conflict occurs, as sometimes it will, the mystical half of the mind will prevail, and the professional half will suffer a few blind spots —but probably not too many or too large to cripple him as a scientific doctor

However, most citizens in a Communist State are not dedicated Communists (any more than most citizens in a democracy are dedicated Democrats or Conservatives), and it is the educated but undedicated who is most likely to become the revisionist, the dangerous liberal, the traitorous reactionary

I suggest that the Government of the People's Republic of China realises full well that it cannot risk educating tens of thousands of young men and women into the habits of critical thought regarding people, and self-reliance in handling people, that a man must have for the successful practice and understanding of modern Western medicine Even less can the State afford to let such hordes of dangerous thinkers loose among the masses I believe that the forcible dilution of Western medicine with old magic is an attempt to produce a new species of medical animal, still capable of acting in a priestly role as comforter of the sick, still capable of practising modern and indispensable techniques according to the book, but without that perilous turn of mind that kicks against the pricks and asks a sound argument for every thesis

APOLOGIA

To Western and non-Communist minds this explanation may appear impossibly far-fetched. The danger to the State that I have conjured up is so nebulous, the remedy so heroic But the curious happenings are there and must be explained Consideration of two relevant circumstances may make my interpretation seem less fanciful

To a true Communist there is only one, supreme, inviolable science, and that is the science of Communism All other facts, disciplines, and behaviours must fit the sacred doctrine, or change to fit, or be abolished What to an unpolitical scientist seems grossest cynicism or illogic, may to a Communist appear as common sense In the Communist vocabulary, expediency is a synonym of truth. I stress this not as political criticism (which is not the purpose of my writing) but to make the point that the assault on medical science taking place in China today is not necessarily inspired by motives that would make good sense to a non-Communist mind Indeed, to the Communist mind, the happenings here described may not appear as an assault at all

The second circumstance is peculiar to China Before the Communist revolution the better medical schools were largely run by foreigners The outstandingly excellent Peking Union Medical College was owned by the China Medical Board, endowed from Rockefeller funds Many of the others of good standing were owned by missionary societies

For years the Chinese had resented foreign management of their affairs, and I have the impression that missionaries were resented more than most, despite their simple wish to serve Because of this foreign hold on medical education and services, the profession in China had closer links with the unpopular West than any other important native group When the Communists drove south and took the land, they must have looked with particular suspicion upon the doctors who had been nurtured by American gold and Caucasian Christians

One last implication The new Chinese medicine can flourish only if its practitioners are kept effectively isolated from Western thought It is difficult to see how isolation can be long maintained whilst both outlooks survive Possibly the active promotion of the one betrays an assumption that the other faces short shrift

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Public Health

ANTIVACCINIAL GAMMA-GLOBULIN IN SMALLPOX PROPHYLAXIS

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GAMMA-GLOBULIN prepared from adult serum has been used successfully in measles prophylaxis for some years, and since 1956 gamma-globulin, prepared from the serum of recently vaccinated or revaccinated adults, has been available, through the Public Health Laboratory Service, for smallpox contacts As yet, however, there is little evidence as to the efficacy of this antivaccinial immune globulin

Field trials were reported by Kempe, Berge, and England in 1956 In Madras, in 1953, 56 household contacts of smallpox cases were vaccinated and given vaccinia immune gamma-globulin, while a control group of 75 household contacts were vaccinated only Of the first group 2 subsequently developed smallpox and 1 died, while in the control group there were 8 cases of smallpox with 3 deaths In the same report evidence is presented of the value of gamma-globulin in the prevention of generalised vaccinial infection in eczematous children who required vaccination or who were exposed to recently vaccinated children

In the Tottenham outbreak of smallpox last year vaccination was supplemented by vaccinia immune gamma-globulin for primary contacts who had not been previously vaccinated

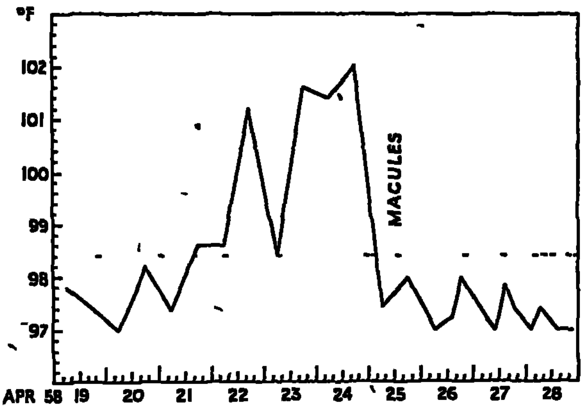

Fig 1—Temperature chart of case 3, J L, aged 6

(Hogben, McKendrick, and Nicol 1958) None of these developed smallpox

The recent occurrence of smallpox on Merseyside provided an opportunity to observe the effect of gamma-globulin, prepared from the serum of recently vaccinated individuals, on close family contacts of the second case

History of the Outbreak

THE FIRST CASE

The *Circassia* arrived at Liverpool on the evening of March 19, having on board a coloured seaman with smallpox He had become ill on March 9, eleven days after leaving Bombay, and the rash had appeared on March 12 On arrival he had a severe confluent pustular eruption He was landed by the fireboat *William Gregson* and taken by ambulance to the Smallpox Hospital, New Ferry By March 24 the lesions were drying up

At the Smallpox Hospital the usual precautions were taken about disposal of scabs, disinfection of floors and disposal of bed linen After the patient's admission no-one entered or left the hospital grounds except medical personnel and the matron of the parent hospital Stores were sent from the parent hospital, milk and groceries were left outside the main gates

THE SECOND CASE

Family L lived in a row of houses about 400 yards from the Smallpox Hospital

The son, T L, aged 1 year and 11 months, unvaccinated, had been confined to his home for a fortnight before March 21, because of mumps On March 25 he was taken by his mother to the hairdresser's On April 6 he appeared to be suffering from a heavy cold and was generally " out of sorts " On April 9 a rash appeared on his face, and next day it had spread to his arms and legs On April 14, at his doctor's request, he was seen by two of us (F S M and E R P), a diagnosis of severe discrete smallpox was made and he was admitted to the Smallpox Hospital The eruption was pustular, semiconfluent on the face, and profuse on the extremities He was extremely ill From admission he was given one million units of penicillin daily On April 18 his condition was still very poor, and 2 5 mg of cortisone in orange juice was given twice daily by mouth for three days On April 20, when the lesions were beginning to dry up, he showed definite improvement, and with the fall in temperature next day cortisone and penicillin were stopped By May 8 most of the crusts had separated, though a few remained on the scalp He was discharged from hospital on May 17

T L had been at home during the first six days of the eruptive stage of his illness and his family contacts had been heavily exposed They were his father, Mr L, aged 37, vaccinated in infancy and during war service, his mother, Mrs L, 40, vaccinated in infancy and again successfully in 1946, his sister, J L, 6, unvaccinated, and his grandmother, Mrs K, 73, vaccinated in infancy These family contacts were vaccinated on April 14 and kept in isolation at home (Other known contacts of T L were vaccinated between April 14 and 16) But J L and Mrs K had been heavily exposed to infection for so long that vaccination seemed unlikely to protect them Immune gamma-globulin was sent by Dr J C McDonald of the Central Public Health Laboratory, Colindale, London, and on April 15 1 5 g dissolved in 12 5 ml distilled water was injected intramuscularly into J L, and 1 0 g similarly given to Mrs K On April 16 a further 0 5 g was given to J L

Reactions to vaccination—Mr and Mrs L both had accelerated reactions maximal about the fourth day Mrs K had the reaction characteristic of primary vaccination, with axillary adenitis, and after nine days the large vesicular take still showed no sign of drying The reaction of J L was also primary in type but without adenitis At eight days she had a small vesicle surrounded by a well-marked areola, but next day this was much less and a central scab had formed—rather earlier than might be expected in a typical primary take

THE THIRD CASE

On April 21, seven days after vaccination and twelve days after the appearance of the focal eruption in her brother, J L had a slight evening rise of temperature

Her temperature chart is shown in fig 1 During these days when the temperature was raised she had no headache, backache, or sore throat, she felt quite well and played at home during the day On April 25, when her temperature had returned to normal, two small red papules were present on her right forearm, one on her forehead, and one macular lesion on the back of her right hand and one on her left thigh Scrapings from the lesion on the back of her hand showed no virus on direct microscopical examination but produced typical variola lesions on the chorioallantois of chick embryos Next day a few more lesions were seen fig 2 shows the position of all the lesions on April 28 From lesions scraped on April 26 and 27 smallpox virus was recovered on inoculated chick embryos The patient had been removed to the Smallpox Hospital on April 26, but she had no further rise of temperature The lesions never developed into typical smallpox pustules, some developed tiny vesicles before drying up and others never progressed beyond the papular stage

Had she not been under daily supervision this child would not have been recognised as a case of smallpox

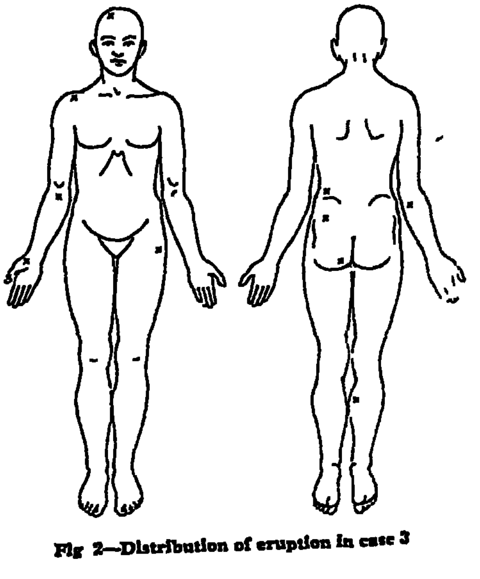

Fig 2—Distribution of eruption in case 3

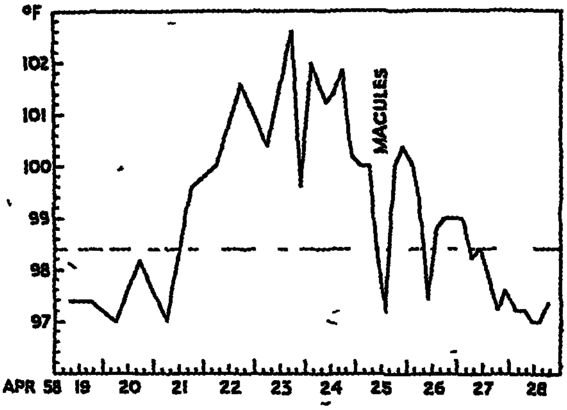

Fig 3—Temperature chart of case 4, Mrs K., aged 73

THE FOURTH CASE

Mrs K., the grandmother, also had a slight rise of temperature in the evening of April 21

Next day her temperature was higher and she complained of axillary adenitis apparently due to her vaccination which was vesicular at this time Her temperature chart is shown in fig 3 On April 23 she had a profuse discrete macular rash and was admitted to the Smallpox Hospital Next day the rash was generalised like that of a severe rubella It was absent from the face, sparse on the hands and feet, but profuse on arms, back, chest, abdomen, and thighs, and confluent over the scapular and lower lumbar region This was probably a prodromal rash Scrapings taken from the eruption on the left forearm failed to show virus by inoculation of chick embryos

On April 25 her temperature was normal and the generalised rash was fading She had a few maculopapular lesions, however—one on each thigh, one on left forearm, and one on the right thumb Scrapings from this last lesion showed virus particles on direct microscopical examination and produced typical variola lesions on the chick chorioallantois On April 28 focal lesions, rather atypical in distribution, were present as shown in fig 4 From lesions examined on the 26th and 27th virus was recovered by chick-embryo inoculation Some of the lesions had become pustular by the 27th and 28th but they dried up thereafter

Although this patient had rather more general disturbance than J L (case 3), and had an extensive prodromal rash, there was no secondary fever and the illness ran a mild course

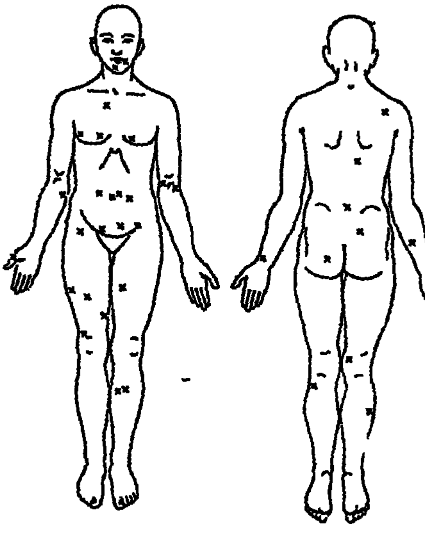

Fig 4—Distribution of eruption in case 4

Garglings

Garglings usually contain virus from about the time that the focal rash appears (MacCallum, McPherson, and Johnstone 1950, Downie and McCarthy 1954)

Garglings had been collected from cases 3 and 4 daily from April 18 to 29th inclusive—i e, from three days before the onset of fever until eight days thereafter They had been kept at −70°C until examined on May 1, 6, and 9 Specimens were spun at 10,000 r p m for thirty minutes, and the deposit (suspended in fluid containing streptomycin and penicillin) was tested for virus by inoculation on the chorioallantois of chick embryos From none of the specimens was virus recovered even by two or three passes of the inoculated membranes to further chick embryos That virus had not disappeared from the specimens during storage was suggested by examination of garglings from case 6 A specimen taken from this patient on the seventh day of illness was heavily infected with virus, and the titre had not diminished after a month's storage of a portion of the specimen at −70°C

Neither case 3 nor case 4 ever showed any obvious lesions in the mouth, and the failure to find virus in garglings suggests that their throat and mouth secretions were not highly infective

THE FIFTH AND SIXTH CASES

As contacts of case 2 had been kept under surveillance until May 1 and no further case had been reported up to May 10, the outbreak was thought to be at an end However, a man, Mr G, aged 54 (case 6) was admitted to Clatterbridge Hospital as a case of meningitis on May 17 He had a hæmorrhagic rash and was extremely toxic He was seen by two of us (F S M and E R P) several hours after admission and recognised as a case of hæmorrhagic smallpox

He was removed to the Smallpox Hospital where he died three days later Material from his skin lesions showed virus on laboratory examination As his wife was known to have been a contact of case 2, this man, who had been vaccinated in infancy only, had been revaccinated on April 16 This vaccination produced no take and he was told by the health visitor, who called daily, that he should report to the clinic to have the vaccination repeated, but he did not see fit to do so His illness began on May 12, but he went to work this day and the next He visited his doctor on May 17 and from there was sent to hospital

His contacts, including those at the doctor's surgery and at the general hospital, were vaccinated, and 9, who had not previously been vaccinated, were given immune gamma-globulin None of these contacts developed smallpox

As the wife of case 6 had visited the home of case 2 just before case 2 was admitted to hospital on April 14, she was examined immediately after the nature of her husband's illness was recognised

On May 18 there appeared to be a few old crusting lesions From three of these, one in the palm of the hand and two on the trunk, crusts were removed and extracted together for inoculation of chick embryos Smallpox virus was recovered This woman (case 5) had been vaccinated in infancy and again on April 15, one day after contact with case 2 This last vaccination gave a good slightly accelerated primary take which left two good scars She had been visited daily by a health visitor until May 1, but no illness had been recorded. On May 1, 2, and 3 she had an influenza-like illness This illness occurred seventeen days after her last possible contact with case 2 and eleven days before her husband sickened

If this woman's illness on May 1–3 was mild smallpox, the incubation period was longer than that usually accepted (ten to fourteen days) and the incubation period of her husband (case 6) rather less than the average

Discussion

This outbreak was one of variola major originating in India The first 2 cases were extremely severe, with semiconfluent eruptions, while the 6th case died of a hæmorrhagic form of the disease It is difficult to assess the prophylactic value of gamma-globulin given to contacts of cases, because of the uncertainty of infection being acquired by such contacts

Only planned experiments such as that of Kempe et al in India can quickly provide conclusive evidence Nevertheless, the observations on cases 3 and 4 suggest that immune gamma-globulin greatly ameliorates the course of smallpox after infection has been acquired These 2 patients, one unvaccinated and one vaccinated over seventy years previously, had been for several days in contact with case 2 before the diagnosis of smallpox was made If one allows for an incubation period of twelve days in cases 3 and 4—although this may have been prolonged by the administration of gamma-globulin—vaccination was not carried out until the fifth day after their infection Primary vaccination at this stage in the incubation period is believed to have little protective value While the immunity response after revaccination may be fairly rapid (McCarthy, Downie, and Bradley 1958) the primary type of take shown by Mrs K indicated that she had little or no residual immunity from her childhood vaccination We believe that the extremely mild course of infection in case 3 and the mild smallpox in case 4 can be attributed to the gamma-globulin given to these patients seven days before their illness, and not to their successful vaccination The absence of virus from their garglings is not altogether surprising since neither patient had detectable lesions in the mouth or pharynx

The dose of gamma-globulin given to case 3 (aged 6) was 2 grammes—twice the dose recommended for adult contacts This represents several hundred millilitres of vaccinia convalescent serum The gamma-globulin used was tested for variola-neutralising antibody by the chorioallantoic membrane technique (McCarthy and Downie 1953) A 1% solution gave more than 50% neutralisation of variola virus in fivefold dilution up to and including the dilution of 1 in 125

Mrs G (case 5) also had a mild infection, but the mildness of her disease can probably be attributed to vaccination in infancy followed by successful revaccination the day after her contact with case 2

Summary

The outbreak of smallpox in Merseyside comprised 6 cases, the first being an Asiatic seaman infected in Bombay

The 2nd case was a boy about 2 years old who remained at home for the first nine days of his illness

In close contact with him were his sister aged 6 (case 3) who had never been vaccinated and his grandmother aged 73 (case 4), vaccinated in infancy

These were vaccinated seven days before the onset of their clinical infection, but probably this had little effect The mildness of their illness is attributed to immune gamma-globulin given on the day after their vaccination

REFERENCES

Downie, A W , McCarthy K (1954) The Dynamics of Virus and Rickettsial Infections, p 194 New York.
Hogben, G H , McKendrick G D W , Nicol, C G (1958) *Lancet*, i, 1061
Kempe, C H , Berge, T O , England, B (1956) *Pediatrics*, 18, 177
MacCallum, F O , McPherson, C A , Johnstone, D F (1950) *Lancet*, ii, 514
McCarthy, K , Downie, A W (1953) *ibid* i, 257
— — Bradley, W H (1958) *J Hyg , Camb* (in the press)

THAT DAMNED WORD HEALTH

I GORDON
M D Edin , M R C P , D P H
MEDICAL OFFICER OF HEALTH, ILFORD

> "Health is a state of complete physical, mental, and social wellbeing, and not merely the absence of disease or infirmity "—
> WORLD HEALTH ORGANISATION

IN considering health we must remember that the problem is biological—not theological, as might almost be assumed from the above definition,[1] or political, as might be supposed from the origins and course of the National Health Service

Man, like other organisms, is evolving continuously, for better or worse, within his environment, and when a person's contact with his environment, internal or external, is deleterious, he is bound to suffer some damage, though this may not be permanent or even appreciable He makes an effort to overcome any disability thus caused, and numberless times during his lifetime each individual moves from apparent defeat to apparent victory An apparent defeat may cause the effort leading to apparent victory, and an apparent victory the lack of effort leading to apparent or real defeat For defeat read illness, for victory, health

To maintain his equilibrium with his environment, man and his species are in perpetual struggle—with microbes, with incompatible mothers-in-law, with drunken car-drivers, and with cosmic rays from Outer Space How then, in this context of movement and buffeting back and forth between organism and environment, can we find any place for the woolly-headed definitions of " positive health ", as a state that can and must be considered apart from disease? It is as if we were to insist on discussing white without mentioning black, hot, without intruding with that dreadful word cold In the living there is no such thing as complete health, any more than there is complete disease (which is death) each organism is somewhere between the two, as each temperature is somewhere between absolute minimum and absolute maximum We all of us have something of disease with us, even if it is only an acne spot today and food-poisoning tomorrow Disease began to corrode us the moment we were conceived, if not before In fact, we may be higher up the ladder of health by virtue of some imperfection, as the life-history of many a handicapped person, has shown, it may be healthy to have something wrong

People who talk about positive health have become confused The " positiveness " of health does not lie in the state, but in the struggle—the effort to reach a goal which in its perfection is unattainable

* * *

This attempt to separate health from disease is of more than academic importance it has had devastating effects on the structure of the National Health Service and other statutory services The local health authorities generally deal with those who are presumed to be well, and the hospitals with the sick, so in the same convalescent home one may find two men, one of whom is sent for recuperation by the local authority and has to pay or be assessed, while the other is sent for convalescence by the hospital and does not have to pay a penny, though he may not be any more ill Even in the one service, district nursing is free and domestic help for the same sick person is not The worst example of the outcome of this false philosophy is that local-authority welfare activities for the aged are separated from medicine Whether a person is "aged and infirm" or "aged and sick" is often a matter of doubt, and may vary from day to day, it is something on which doctor may differ from doctor, or doctor from welfare officer Yet on the opinion which prevails the old person may receive accommodation or be denied it—may be made to pay or freed from monetary worries Even the expectant mother bears a smaller financial burden if she enters a maternity hospital than if she is confined at home

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[1] See also A Study in the Epidemiology of Health , published by the Kent Pædiatric Society from 11, Brampton Road, Bexleyheath Kent.

When the B B C produced its programme "Your Life in Their Hands," the *British Medical Journal*[2] accused it of concentrating on "disease education" It suggested that disease should not be discussed on television, where the emphasis should be on health But of course it is quite impossible to discuss health with intelligent people without simultaneously discussing disease Are we to tell the inquiring student of health not to smoke without describing bronchitis or cancer of the lung, or what to eat without telling him about scurvy, rickets, or beriberi? The *British Medical Journal* points out that the operative word in the National Health Service is *Health*, as if this somehow disguises the fact that fundamentally it is a bed-and-bottle service Even the World Health Organisation, in spite of its name and its erroneous definition of health, concerns itself (and quite rightly) mainly with disease, as does the Ministry of Health

Medical officers of health themselves are not always clear about the impossibility of separating health from disease. They, and the Ministry of Education, tend to evaluate school medical inspections by the number and accuracy of the defects noted if none are noted, either the examining doctor didn't do his job properly or the child was perfect It is not so, all children have defects, and the fundamental job of the school medical officer at a routine examination is to decide which are significant and to inform the parents accordingly. The lists of defects that obsess clerical staffs and the Ministry are but a minor, inaccurate, and variable excretion of a very important (even though hurried and harassed) medical examination Inasmuch as this evaluation of the indefinite borderline between health and disease concerns every child, such work is even more important than the highly specialised technique of advising the obviously handicapped

My colleagues in public health have tended to adopt the fashionable view that "health" is a more noble term than "medicine" because the latter implies contact with disease Hence the imaginary elevation of the School Medical Service to the School Health Service However, they are now coming to regret this, for Health does not pay as well as Medicine (i e, disease), nor are its exponents as well respected. The sooner the Society of Medical Officers of Health insists on using the terms "community medicine" or "community physician" in its title, and drops the word "health", the earlier will it command the attention it deserves in the nation's counsels Let the word health be the prerogative of the Royal Society of Health and the Public Health Inspectorate, and others whose training and function are not intimately connected with disease

* * *

When there is discussion of "positive health"—a state to be considered apart from disease—in the words of the late but unlamented German field marshal, "I reach for my gun"

In England Now

A Running Commentary by Peripatetic Correspondents

Charles was always a bit of a devil for making a clean sweep Perhaps some radical streak in his nature led him to take up surgery Perhaps the disciples of that art are inclined to favour total extirpation of any pretty frills that stand in the way of stark function It all seemed rather heroic from my end of the table I used to give dopes for Charles in the old rag-and-bottle days, and I remember watching him open up an abdomen that had defied the diagnostic skill of physician and surgeon alike In went his hand for the lucky dip, out popped a rather seedy looking appendix Charles eyed it with distaste. Its obvious chronicity offended his dignity by all rights it should have burst during the attack before last, but it did not it lay there across his finger and sneered back Charles performed his usual pretty appendicectomy as a side-line to a dissertation on downdraught carburettors, and pushed the rest back He rummaged about in the pelvis and his eyes lit up With some difficulty a fibroid uterus was coaxed out under the floodlights, and we were treated to a gynæcological exhibition turn for the next twenty minutes After the hysterectomy I was getting ready to doze off myself with the warmth and the ether fumes, when Charles complained profanely that the patient was not relaxed enough for him to get on with the original aim of an exploratory laparotomy I sighed and Mrs Ugglethorpe sank deeper into oblivion Her gallbladder was rattling like a dice-box with stones, so she lost that little lot. There was rather a hollow echo as her abdominal wall was stitched. She could never complain that she had not had her money's worth Actually she did very well afterwards, but that is beside the point

Charles lives about thirty miles outside Town, and has the sort of garden that consultants are expected to have He also has no gardener Twin carburettors and an elegant suite of rooms in Wimpole Street are completely neutralised if appearances are not kept up at Riverside Lodge The grass was too long and tough for a mower Charles did not think that his lumbar discs would endure sufficient torsion for the good old-fashioned scythe Mary refused downright to get on her knees with the shears, and managed to persuade him to hire the mechanical scythe from the golf club On Sunday afternoon he started it up and trundled the thing chattering towards the lawn. It made a grand job right across the mid-line We waited for Charles to swing it round the other way he was red in the face and running by then the engine was roaring, so was Charles Straight over the rose beds they went Fanny Blankers-Koen was overtaken, Mrs Sam McGredy was cut off in her prime, General MacArthur fell to the sword, Anne-Else and Karen Poulsen were guillotined in one unhappy family group On through the borders in front of the house Azaleas, red hot pokers, carnations, and delphiniums fell in piles So did *Hamamelis mollis* I had visions of Mary being trapped against the wall and serially sectioned by the runaway microtome, but, with a last despairing wail, Charles tugged at the offside handlebar and then let go The aid to surgery fell into the river

I was most unpopular for mentioning Mrs Ugglethorpe.

* * *

Malaria is not a disease which one expects to see every day, or indeed every other day, north of Hadrian's Wall I was slightly taken aback, therefore, to be summoned by my Chief to see a case of malaria late one evening

By the time I arrived he had departed and I was left with the problem But the blood-film confirmed the diagnosis, and only the knowledge that the Chief had been a classical scholar in his youth prevented me from sending him a telegram Veni, Vidi, Vivax!

* * *

Mrs. McLaren, despite her name, was French She was in her 76th year, immensely entertaining, and remarkably vivacious for a woman of her age. Unfortunately her gallbladder was full of stones and she had been admitted because of recurring attacks of severe biliary colic Operation was advised and was firmly refused for no very definite reason I resolved to make a final persuasive effort but she shook her head and said, " I am very stubborn, my mother used to say I was the most stubborn woman in Paris "

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[2] Brit med J 1958, i, 510

Then I remembered the charming Oscar Wilde story of the lady who prided herself on her lack of beauty Bravely embarking on my patient's native tongue I began the tale " Dites-moi, Monsieur, si je ne suis pas la femme la plus laide a Paris ?" " Mais, Madame, dans tout le monde!" Wilde, the kindest of men, recorded that the lady was delighted So was Mrs McLaren Almost embracing me, she cried, " Très bien, Monsieur le Docteur, tres bien My gallbladder, it is yours "

* * *

For the annual general meeting our society usually manages to muster some 5% of its membership, consisting of the executive committee plus a few rash youths who lack enough intelligence to understand that regular attendance at annual meetings (i e , attendance at two consecutive meetings) carries a grave risk of nomination and unanimous election to the executive Myself, I was very shabbily treated As a newcomer I attended two A G M 's, but when I skipped the third I was nominated and elected to the executive *in absentia* The first I heard of this was 10 months later, when I was summoned to the next meeting of the executive Sense of responsibility made me attend subsequent meetings, until after about 7 years I realised that all of the older members had " been through the chair " While I was vice-chairman, I was reprieved when it was suggested that the chairman should hold office for a further year This had happened only once before , but I was prepared to ignore the apparent insult, in return for not having to officiate at our first annual dance

You see, I last went to a dance shortly before the war In those days I was courting hard, and affected a personal version of the soft-shoe-shuffle But 19 years is a long time, something had to be done despite the year of grace After 11 months of procrastination, and an urgent phone call to a local dancing academy, I attended a " private lesson " session Everyone was very kind to me One lesson taught me the rudiments of a slow waltz, and one the basis of a quickstep Each night I lay awake, twitching, one, two, together or slow, slow, quick-quick slow

When the great day came, of course there were so many people there that, whatever their abilities, there was no room to do more than the old soft-shoe-shuffle (What is the use of learning to dance if on the floor one cannot go ahead on a north-north-westerly bearing for another two yards, without hazarding the ship and sinking with all hands on each leg of the course ?) By 11 P M I was ready for bed by 1 A M I was out on my feet, the only sign or symptom of continuing consciousness being a splitting headache At 2 A M I was allowed out to relieve the baby-sitter My halo lay heavily on me when I found that everybody seemed to think that I had enjoyed the proceedings as much as they had

I really must get on with these dancing lessons in good time this year The duties of chairman at such a function are hardly onerous enough to excuse him from taking the floor at all

* * *

Perhaps it was subconscious confusion which led a pupil midwife in answering a question about the virtues of breast-feeding to write, " The breast-fed baby is more contented as it lies curdled in its mother's arms "

* * *

Junior Partner I thought you said you believe in telling the patient the truth

Senior Partner So I do

J P Then why did you tell Mrs *P* that she had a strong heart ? In fact you said she has an " exceptionally strong heart "

S P So she has

J P How can she, when she's had coronary thrombosis twice and has a blood-pressure at least double your own ?

S P My boy, any heart which can support a blood-pressure of those dimensions after two thromboses must be exceptionally strong!

Letters to the Editor

UBIQUITOUS STAPHYLOCOCCUS

SIR,—We are all, now, familiar with the ubiquity of the staphylococcus in the hospital air and dust and with its deadly characters So much has in fact been written and so intense has been the attack on typing and categorising the organism that we are rapidly losing sight of the most urgent need—a return to the practice of aseptic method

I have recently made post-mortem examinations on patients who, having survived postoperative pulmonary embolism, have died with staphylococcal abscesses within the pulmonary infarcts In some of the cases there had been a staphylococcal wound infection in the immediate postoperative period

Bacteriological examination of necropsy material, so often neglected, continues to provide a sinister reminder of the omnipresence of the staphylococcus and points clearly to the remedy—aseptic method

This remedy will prove expensive in staff and materials Nevertheless it must be applied sooner or later We are asking too much of the human body and its powers of resistance to injury when we add to deadly pulmonary embolism the mortal blow of staphylococcal toxæmia

Department of Pathology,
University of Cambridge G A GRESHAM

IMPORTANCE OF INTRAVENOUS INJECTION OF DIPHTHERIA ANTISERUM

SIR,—I read the article by Dr Tasman and his colleagues [1] with considerable interest They suggest that the intravenous injection of antiserum in patients suspected of having diphtheria ought to replace the still common practice of giving it intramuscularly, for the following reasons

(1) 100% of the highest antitoxin titre is obtained *the first* day after the injection

(2) The saliva contains antitoxin after only 30 min

(3) The advantages of intravenous injection were clearly illustrated by the protection of guineapigs injected with lethal doses of diphtheria toxin

I think, however, that their process of reasoning is not altogether free from criticism

(1) The intravenous injection of a certain amount of antiserum gives 100% of the highest titre (how many antitoxin units in the blood ?), when given intramuscularly only 50% (table II, p 1299) If, however, we inject intramuscularly twice as much antiserum, or more, the antitoxin titres the first day after the injection may be the same

(2) The early or late excretion of antitoxin in the saliva is not a significant phenomenon, if antitoxin titres in the blood are adequate they neutralise the absorption of the toxin with the saliva

(3) The experiments on guineapigs cannot be transferred to man the moment of infection is not known, and in the experiments with guineapigs the same doses of antitoxin have been used in intramuscular and in intravenous injections Another experiment, giving the guineapigs twice as much antitoxin intramuscularly, might be profitable

On the question of anaphylaxis, I do not think any test gives 100% guarantee of safety Although in my clinic we use a well-purified antiserum only intramuscularly, never omitting the skin test, and although we inject the antiserum in small doses at intervals, we have had a few rare instances of serious allergic reactions

The amount of antiserum injected for diphtheria varies considerably in different countries and is often based on tradition, or on more or less statistically evaluated results of treatment, but we have no exact theoretical means of estimating the amount of antitoxin really needed.

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[1] *Lancet* 1958, i, 1298

Clinic for Infectious Diseases of Childhood,
Warsaw
J. BOGDANOWICZ

TREATMENT OF BREAST CANCER

SIR,—The declared object of radical mastectomy as well as of limited mastectomy plus subsequent radiotherapy is to eradicate all tumour tissue from the chest wall and from the axilla.

Success or failure may or may not be reflected in the five-year-survival rate, which is influenced by such other features as clinical stage and histological character of the tumour. The effectiveness of these treatments could, however, be expressed by stating the proportion of patients who (*a*) remain free of any clinical manifestation of the disease on the chest wall or in the axilla for five consecutive years after the first intervention, (*b*) die within five years without such manifestation (of metastases), (*c*) survive for five years but show disease on the chest wall or in the axilla; (*d*) die within five years with, but not necessarily of, disease on the chest wall or in the axilla.

These results should be stated for each of the various stages according to a simple (Steinthal) classification. Such information from those who are in a position to analyse a large number of cases would present a more rational basis for advice on appropriate treatment than many of the statistics which have little clinical significance.

Radiotherapy Department,
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London, W.2.
M. HULBERT

CHLORPROPAMIDE

SIR,—I am interested in the account of the trials of chlorpropamide reported by Dr. Murray and his colleagues in your issue of Sept. 13. Unfortunately my experience in treating a similar group of 43 diabetics has not been correspondingly satisfactory, nor yet as good as mine with the generally abandoned carbutamide.[1]

The investigation began in February, 1958. 43 diabetics had chlorpromazine, but only 3 were under observation as inpatients. There were 11 men and 32 women. The choice of case and the conditions under which they were treated were no different from those under the now familiar tolbutamide therapy. Only 3 patients were under 50 years of age. 23 patients had been diabetic for less than two years and 20 for longer, up to 23 years; previous treatment had been by insulin in 21, tolbutamide in 3, and diet alone in 19.

Dosage.—In the earlier cases 0.5 g. of chlorpropamide was given three times a day after food, with a smaller maintenance dose. As our experience increased, the initial dose was reduced and the later cases in the series received only 0.5 g. or 0.2 g. daily in a single dose after breakfast. A fall in blood-sugar to below 200 mg. per 100 ml. occurred in 38 cases and was maintained at a satisfactory level. Actual hypoglycæmic symptoms were recognised in 1 case only. In 6 patients there was inadequate or no hypoglycæmic effect, and in 1 man who appeared to be doing well an intercurrent bladder infection associated with a carcinoma necessitated a return to insulin in high dosage.

Of the 14 diabetics still maintained on an appropriate diet and chlorpropamide, only 1 is taking more than 0.5 g., and it is possible that those taking less may eventually be controlled on diet alone. 3 of the patients who later responded satisfactorily suffered considerable nausea, anorexia, and burning epigastric pain until the dose was reduced.

Reasons for discontinuing treatment.—The hypoglycæmic effect was inadequate in 6 cases (16%). Intercurrent infection or other illness made it imperative to return to well-tried and predictable methods of treatment in 4 cases. In 7 new diabetics when chlorpropamide had been used for initial control, diet only was the method of final choice. Since my earlier brief report to the International Diabetes Federation in Dusseldorf in July, mentioning the toxic effects we had observed, 4 other cases have occurred on low dosage of the drug. Nausea, anorexia, and vomiting were unpleasant in 15 patients, and in 9 of these vertigo was severe and nystagmus was demonstrable. Dermatitis occurred in 2 patients, associated depression and insomnia was particularly marked in one man, although he gave full credit to the drug for having rid him of his glycosuria. One woman persevered but eventually admitted that however much she disliked having injections of insulin it did not make her feel sick like the tablets. A man of 72 who had been transferred from tolbutamide to chlorpropamide with moderate success for three months suddenly began to vomit and continued for three days until the drug was completely withdrawn.

It is possible that these symptoms may be more severe in ambulatory patients than in a trial conducted on inpatients, but such are the conditions in which such a drug would come to be used. It was found that there was a lowering of the total leucocyte count, but when differential counts were performed no reduction of the polymorphs was noted.

Leicester
JOAN B. WALKER

CHILDREN IN HOSPITAL

SIR,—As a psychologist and psychiatrist working in a long-term hospital (mainly orthopædic) for children, we should like to make a few comments on Professor Illingworth's article (July 26) and subsequent correspondence.

Everyone would agree that contacts between children and their families should be maintained as far as is reasonably possible. We cannot lay down any general rules because we simply do not know whether the advantages to the children and parents of frequent visiting outweigh the disadvantages in terms of parental anxiety, neglect of other children and husbands, and the unhappiness of unvisited child patients.

The advocates of frequent visiting at all costs seem to base their claim largely on the careful work of Bowlby et al.[1] But Bowlby and his coworkers were not concerned with the effects of visiting on children in hospital. The implicit assumption by those who base their claims for frequent visiting on Bowlby's findings seems to be that frequent visiting will at least alleviate the separation anxiety of mother and child. This seems commonsense, but it may be an unwarrantable jump (cf. the differing views of experts on this point).

It seems to us legitimate to assume that very frequent visiting of all the children in a long-stay hospital (especially when, as at Chailey, patients come from all over the British Isles) is not possible. O'Connor[2] writes: "There is some danger that too great stress on the dangers of mother-child separation may divert interest from the development of research into the optimal cultural conditions for infant intellectual and emotional growth." Similarly, too much stress on mother-child relationships in hospital may divert attention from developing the optimal conditions for children, particularly in long-stay hospitals. Some children are not in fact permanently damaged by early separation from their homes—36% of Bowlby's sample were rated as "adjusted" after their return from hospital, and many of those rated as "maladjusted" showed milder symptoms than was expected. It has been found that some institutions have a beneficial effect on children. It should perhaps be remembered that the basic assumption underlying the present policy of the school health service for the rehabilitation of maladjusted children in hostels and residential schools is that emotional damage in a child can be repaired away from home.

The effect of deprivation in early childhood may not be as lasting as was at first thought. Work with the rehabilitation of young adult defectives supports this[3] Given a sound environment, children tend to adapt Illingworth stresses the importance of gearing hospitals to the needs of children and makes important suggestions on training personnel and on equipment

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[1] Walker, J. B. *Brit. med. J.* 1956, ii, 657.

[1] Bowlby, J. Maternal Care and Mental Health. W.H.O. Monograph Series No. 2. Geneva, 1951. Bowlby, J., Ainsworth, M., Boston, M., Rosenbluth, D. *Brit. J. med. Psychol.* 1956, 29, 211.

[2] O'Connor, N. *Acta psychol.* 1956, 12, 174.

There appear to us to be two lines of approach to this problem One is to gear the hospital to all the needs of children, as far as we know these at present, the other is to try to influence public opinion so that there is in general a more favourable attitude towards the physically handicapped It has been shown in America that physically handicapped children tend to show more psychological difficulties than physically normal children, irrespective of their placement, and one reason suggested is society's attitude towards the physically handicapped[4] Bowlby knew that his findings might be at least partially accounted for by the psychological effects of illness per se

To sum up there is some evidence to suggest that some children in hospital are not adversely affected emotionally, that some institutional placements can have a beneficial effect on development, and that unfortunate early experiences (including separation or admission to hospital) do not always have irreversible damaging effects The development of optimal conditions for children in long-term hospitals can do much to minimise psychological trauma The dangers of separation due to illness can be over-emphasised, and so cause avoidable distress to families and to hospital staffs

Chailey Heritage
(Craft School and Hospital),
Chailey, Sussex

ELSPETH STEPHEN
ELIZABETH WHATLEY

ACADEMIC REVOKE

SIR,—One of Dr Spencer's conclusions (Aug 30)—namely, that students displaying academic revoke are predominantly of fat and muscular physique—hardly seems to follow from the data which he presents

Referring to his fig 1 he observes "It will be seen at a glance how work revokers congregate to the left of the somatotype chart" *Simple counting of the cases to the left and right* of the vertical line yielded 11 revokers to the left, 10 to the right, and 1 on the midline

If it was intended that the left and right were to be taken from perpendiculars to the ectomorphy axis, the figures on my counting are as follows

	Revokers	*Other psychiatric cases*
Ectopenic	13	26
Ectomorphic	9	52

This table yields a χ^2 of 4 79, which is significant at the 0 05 level,[1] and which confirms Dr Spencer's claim of an association between a fat and muscular physique (ectopenia) and the tendency to revoke This, however, is true of his *particular sample*, and cursory examination of his fig 1 as well of the above table makes it clear that his population of psychiatric cases is predominantly of ectomorphic physique Any group of cases of normal physique could therefore be expected to differ from the non-revoke part of his sample

If Dr Spencer wished to determine whether his revokers were predominantly of ectopenic physique the appropriate comparison would seem to be

	Revokers	*Expected numbers (on a 50 50 basis)*
Ectopenic	13	11
Ectomorphic	9	11

This table yields a χ^2 of 0 73, which indicates roughly a 40% probability[5] of obtaining a greater proportion of ectopenics on subsequent sampling of a population, where the true incidence of ectopenics and ectomorphics is equal Hence we cannot conclude that the revokers tend to be any more ectopenic than ectomorphic, and must conclude, on the evidence presented, that they are of normal physique in these respects, as contrasted with the other types of psychiatric cases

Similar considerations could well apply to the relationship between academic revoke and extroversion If extroversion is associated with ectopenia, and intraversion with ectomorphy, then a group of normal physique could be expected to be more extroverted than a psychiatric group of predominantly ectomorphic physique

In conclusion, Dr Spencer has shown that academic revokers differ from other student psychiatric patients in *certain respects It does not follow that revokers would* differ from students in general, in these respects, nor that the correlations would hold good in a general sample of students

Child Study Centre,
41, Brunswick Square,
London, W C 1

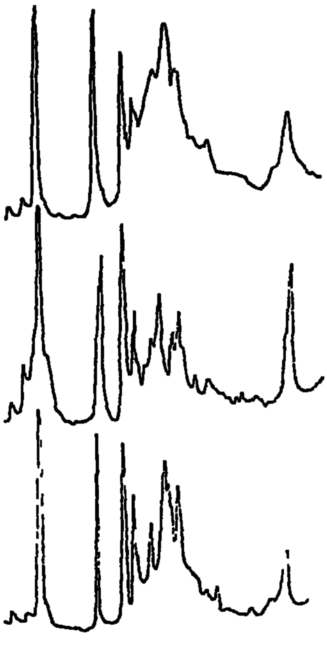
COLIN B HINDLEY

BACTERIAL RESIDUES IN SARCOID LESIONS

SIR,—Mr Nethercott and Dr Strawbridge[1] stated that they had demonstrated mycolic acid in extracts of sarcoid lymph-node This identification was based in part on the acid-fast nature of the extract and in part on a spectroscopic similarity between the extract and a substance called wax C of the human strain of tubercle bacilli

From experience we have gained in the fractionation of the lipids of many strains of tubercle bacilli and in the identification of the isolated components by means of their infra-red absorption spectra,[2] we feel that insufficient evidence has been presented for the identification of mycolic acid in the extracts of sarcoid lymph-nodes

The infra-red spectrum of wax C recorded in the paper of Nethercott and Strawbridge is readily identified as phthiocerol dimycocerosate and contains no apparent mycolic acid The spectrum of the lymph-node extract is similar to the spectrum of any triglyceride of the type found in lard or butter To further illustrate the lack of specificity of the compound isolated from sarcoid tissue, we have prepared a similar extract from lymph-node in a case where the postmortem diagnosis was acute leukæmia A sample of abdominal fat was also extracted The infra-red absorption spectrum for the lymph-node extract is shown in the accompanying figure together with spectra of phthiocerol dimycocerosate and mycolic acid The spectra of these three substances are sufficiently reproducible for it to be readily stated that they are three distinct substances each of which can be recognised by its characteristic spectrum The spectrum of abdominal fat (not shown) was similar to that of the lymph-node extract



Infra-red absorption spectra of various lipid substances Top, *lipid extract of lymph-node from leukæmic individual*; middle, mycolic acid; lower, phthiocerol dimycocerosate

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[3] Clarke, A D B, Clarke, A M *Brit J Psychol* 1954, 45, 173
[4] Meyerson L in Psychology of Exceptional Children and Youth (edited by W Cruikshank) London, 1956
[5] Fisher, R A, Yates, F Statistical Tables Edinburgh, 1953

[1] Nethercott, S E Strawbridge, W G *Lancet* 1956, ii, 1132
[2] Smith, D W Randall, H M, Gastambide-Odier, M M, Koevoet, A L *Ann N Y Acad Sci* 1957, 69, 145

Concerning the identification of the presence of mycolic acid by staining techniques, we have stained by the hot-carbol-fuchsin method the following substances phthiocerol dimycocerosate, butter, petrolatum (M P 52-56°C), carbowax (M P 34-38°C), lecithin, boiled linseed oil, collodion, paraffin, mineral oil, and cholesterol We find that the following substances resist decoloration by acid alcohol and therefore are acid-fast petrolatum (M P 52-56°C), boiled linseed oil, and collodion

On the basis of these observations we believe that Mr Nethercott and Dr Strawbridge have presented insufficient evidence to prove that mycolic acid has been detected in extracts of sarcoid lymph-node

D W SMITH
University of Wisconsin. H M RANDALL

PROTECTION OF GONADS FROM RADIATION

SIR,—The article by Mr Newman in your issue of Sept. 6 on slipping of the upper femoral epiphysis was an interesting reminder of the necessity for taking the so-called lateral (or " frog's leg " position) radiograph in painful conditions of the hip in children

May I, Sir, make a plea for more protection of the gonads from radiation in these cases ?

My practice is to take a normal anteroposterior film without protection, as some of these difficult cases turn out to be an osteochondritis of the ischiopubic ramal junction. All subsequent films, including the first " lateral " view taken, have some screening of the gonads This screening does not detract from the quality and usefulness of these subsequent radiographs All follow-up films of the hip, and the films taken at the time of the pinning operation, should have gonadal screening

General Hospital, Harrogate M. W P WARD

ACCIDENTAL HYPOTHERMIA

SIR,—I have recently seen a case of endogenous hypothermia (rectal temperature 84 5° F) in a woman of 45 years with schizophrenia She had been admitted to hospital with a provisional diagnosis of myxœdema coma I was struck by the similarity of the clinical picture to that described by Dr Emslie-Smith (Sept 6) It would be interesting to know if his patient had a family or personal history of mental illness or if schizophrenia was one of the provisional diagnoses made during the course of her illness

Though the diagnosis in our case was unequivocal from the clinical, biochemical, and necropsy findings, we did, at the time, regard the electrocardiogram with its high-voltage complexes and upright T waves as further evidence against a diagnosis of myxœdema coma Thanks to Dr Emslie-Smith's paper it is now clear that the tracing with its broad-based QRS complexes and J deflections was, in fact, the classical tracing of hypothermia and nothing more It is a remarkable finding that hypothermia should render the electrocardiogram so specific in some respects and yet so non-specific in others that the pathognomonic appearance of euthermic myxœdema coma is lost

Though one can have no real objection to the inclusion of myxœdema hypothermias under the general heading of " accidental ", since the term means happening by chance or undesigned, as distinct from induced or artificial forms of hypothermia, nevertheless one cannot help but have some misgivings on the ground of possible ambiguity The term " accidental " has a certain subconscious association with an accident because an accident is a common cause of an accidental occurrence, and the original cases described under the term were examples of exogenous hypothermia following on some accident, either sudden external trauma or sudden internal catastrophe When one speaks of myxœdema hypothermias one understands endogenous hypothermias, unless stated to the contrary, and in grouping them under the same heading as exogenous hypothermias there is danger, firstly, of thinking myxœdema hypothermias to be of the exposure variety and, secondly, of concluding in general terms about two essentially different forms of hypothermia Particularly is this so in relation to the question of warming

The ever-increasing reports on various types of hypothermia make a classification of the subject desirable and suggest a classification of adult hypothermia on more fundamental lines than induced and accidental Hypothermia may be divided into endogenous and exogenous varieties Endogenous can be subdivided into types due to central nervous dysfunction and types due to endocrine gland dysfunction Exogenous can be subdivided into natural (or spontaneous) and artificial (or induced or therapeutic) Natural can be further subdivided into immersion and exposure types and artificial into medical and surgical types The exogenous hypothermia due to natural exposure would correspond with the cases originally described under " accidental "

Coventry DONOUGH MOYLAN

INDUSTRIAL MEDICINE AND GENERAL PRACTICE

SIR,—I read Dr Keatinge's letter in your issue of Sept 6 with interest because I felt that the leading article in *The Times* of Aug 4 was very special pleading It suggests that the Harlow scheme could be adopted for most towns in which are small industrial units and emphasises the advantage of general practitioners thus looking after their own patients

Harlow is a small new centre with work, home, and doctor closely knit In most areas of this country the scatter is wide Most general practitioners doing industrial work would inevitably be looking after the patients of other doctors In many families today members are registered with different doctors, and in a group practice, which is recommended, a group of doctors look after the same family In this development where does the family doctor come in ?

The Times article makes no reference to the duties of the appointed factory doctor This statutory work accounts for a major part of the time of general practitioners spent in industry, and has aroused considerable criticism, though the work presents unique opportunities for the advancement of health I venture to refer to my own study[1] of this problem, concerning which the King George's Jubilee Trust in their report *Citizens of To-morrow* recorded " it seemed to us that national development might well be based on a pilot scheme of this nature "

Finally, reference is made to the need for whole-time medical officers in the larger firms to study toxic hazards and environmental conditions, but there is no mention of the need for these problems to be met by occupational hygiene laboratories working on a regional basis, preferably associated with a university This has been done in the U S A and other countries Expert advice is then readily available for all doctors working in industry or elsewhere and also for employers and even employees who think their health may be affected by environmental conditions

Farnham Royal, Bucks M E M HERFORD

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[1] Herford, M E M Youth at Work London, 1957

THE FRONTIERS OF MEDICINE

SIR,—I have read with interest Prof C H Stuart-Harris' article of Aug 30 like those of the celebrated egg, parts of it are excellent, but I resent very deeply his statement "When I was a student, it was common to feel that patients were admitted to the medical wards to lie and rot The great watch-word was 'masterly inactivity' " (Dr Stuart-Harris qualified as recently as 1931) I should like to ask him (a) whether his insult is intended only for the physicians of the hospital where he was a student or for British physicians in general, and (b) whether he thinks that his opinion is widely shared by the large numbers of whole-time professors and lecturers who are now mainly responsible for the training of young doctors

Belfast ROBERT MARSHALL

ATTEMPTED SUICIDE

SIR,—It is impossible for authors to defend themselves against an anonymous review, even if they feel that their work has not received a fair appraisal They have, however, the right to protest against misquotations I am referring to the review (Sept 6) of the book *Attempted Suicide* In this and other books the term " suicidal act " has been used for both suicide and attempted suicide According to your review it was used only for the latter, which is quoted as having been regarded by the authors as not self-destructive No such nonsense was asserted in the book On the contrary, it was made quite clear that every suicidal act aimed at self-destruction but that the suicidal attempt could not be fully understood if this motivation alone was taken into consideration

Sheffield, 10 E STENGEL

*** We much regret that our brief summary of the views of Professor Stengel and Miss Cook should have misrepresented them Most authors will sympathise with him about the difficulty of defence against criticism in review, but this is no greater when the review is editorial than when it is personal Our reviews, like our annotations and leaders, can be challenged —ED L

EFFECT OF INACTIVATED SERUM ON COLD AGGLUTININS

SIR,—From the studies of Boorman and Dodd[1] we learn that human serum can enhance the activity of immune isoantibodies when it is used as a diluent instead of saline Also in other immune systems (immune serum anti-sheep-red-cells or in Rose's test for rheumatoid arthritis) human serum reveals this property I have investigated whether normal human serum retains this property also in the titration of autoantibodies, and I chose the cold agglutinins as more readily titrable

If fresh serum is used instead of saline, the titre of the cold agglutinins increases but little, while if a previously inactivated (at 56°C for 30 min) serum is used, there is a huge increase in the titre (from 1 4000 to 1 16 million in one case, and from 1 1000 to 1 4000 in another)

The use of albumin or human gamma-globulin instead of serum does not bring about the phenomenon Serums devoid of properdin have given similar results, as have also normal serums that have not been inactivated but kept at −20°C for one to two months

Not all human serums show this considerable activation of the autoantibody titre some, in fact, are incapable of producing it, while others increase the titre only slightly

It has not so far been possible to discover whether the phenomenon is due to the presence of an activator or the disappearance of a serum inhibitor any such inhibitor, which disappears at a temperature of 56°C maintained for 30 min. may be represented by a heat-labile fraction of the complement (C^1 or C^2) which is destroyed at that temperature

Institute of Medical Pathology,
University of Genoa
V ROSSI.

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[1] Boorman, K E, Dodd, B E *J Path Bact* 1947, 59, 95

INTRAGASTRIC INFUSION

SIR,—In 1956, you were good enough to publish a short communication[1] about intragastric infusion in infants with acute dyspepsia

We have now used this method 140 times in infants, mainly for acute gastroenteritis We gave physiological saline, Ringer's or Darrow's solutions, and 5% glucose solution, the amount and proportions being the same as for parenteral infusions Sometimes we added plasma substitutes Sometimes plasma was given intravenously In milder cases gastric infusion was combined with feeding by mouth or through the tube We used polyethylene and rubber tubes, as thin as possible, passed through the nose We have not seen any serious complications, even after leaving the tube in for several days

*The effect on vomiting was striking In severe gastro*enteritis the rehydratation was often slower than by the intravenous route, but sometimes the result was almost equally good In toxic gastroenteritis gastric infusion was used only after improvement had been achieved by intravenous infusion Several times we had to replace the method by the intravenous one, either it was not suitable at all or the composition of fluids was wrong

Intragastric infusion has proved a valuable therapeutic measure, and vomiting of any origin very seldom resists this treatment I should be glad to hear from any of your readers who have had experience of enteral infusions

State Hospital, Children's Department,
Děčín, Czechoslovakia
S J HAVELKA

CARDIAC OUTPUT AND RENAL BLOOD-FLOW IN SEVERE DEHYDRATION

SIR,—It is generally supposed that an inadequate general circulation is associated with a reduction in renal blood-flow which is disproportionate to the reduction in cardiac output Renal blood-flow has been determined in most cases by the clearance technique, though this seems an unreliable method when the diuresis is low, as in dehydration

We compared, in serial simultaneous determinations, the cardiac output (by the dye-dilution technique) and the renal blood-flow (by measuring directly the renal venous outflow) in narcotised dogs dehydrated by ligating the pylorus 72 hours before the experiment The reduction in cardiac output was greater than expected from the fall in arterial pressure, so that the total peripheral resistance had increased As determined by the direct technique there was a small decrease in the absolute value of renal blood-flow and the calculated renal vascular resistance was somewhat increased The decrease in renal blood-flow was nearly proportional to the diminished cardiac output

Thus the renal fraction of cardiac output did not decrease during dehydration, as compared to the renal fraction determined by the same technique in normal dogs On the basis of the *p*-aminohippuric acid clearance and extraction ratio a substantially reduced renal fraction was found The clearance results suggested a nearly total renal ischæmia and an enormous increase in renal vascular resistance

A detailed account of our data is to be published in *Acta medica hungarica*

Physiological Institute,
Medical University,
Budapest
P BÁLINT
J STURCZ

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[1] Havelka, S J *Lancet*, 1956, ii, 1312

Obituary

JAMES BENNETT HANCE

K.C.M G, K C I.E, O.B E, M.A, M D Cantab, F R.C S E

Sir Bennett Hance, whose death we announced last week, was already known throughout India as a surgeon and clinician before promotion in 1940 brought him to administrative rank His success in this new sphere was recognised by his appointment as director-general of the Indian Medical Service in 1943 His successful tenure of that post ended with the British withdrawal from India, but he continued his work for both countries as medical adviser to the Commonwealth Relations Office

He was born at Liscard, Cheshire, in 1887, the son of a Liverpool barrister, and he was educated at Oundle School, Cambridge University, and Guy's Hospital After qualifying in 1911 he spent some time in Liverpool as assistant to Prof Blair Bell, who fostered his interest in gynæcology In 1912 he entered the Indian Medical Service with the hope of becoming a teaching gynæcologist on the civil side of the service But the 1914–18 war upset this plan, and after service in France and with the South Persian Expeditionary Force he joined the Foreign and Political Department. As a result he spent the greater part of his service in Waziristan, on the North West Frontier, and in the Princely States of Jodhpur, Rajkot, and Mysore While he was resident surgeon in Mysore his chief hospital was at Bangalore, where he tackled not only his favourite gynæcological problems but also all branches of major surgery, including his latest enthusiasm—orthopædics In 1940 the clinician reluctantly gave way to the administrator, and he entered British India, almost as a stranger, to become inspector-general of civil hospitals in Central India. In 1942 he was moved to Delhi as deputy director-general of the I M S, when his administrative gifts were quickly recognised, and a year later he succeeded Sir Gordon Jolly as director-general

Walter Stoneman

Even in the midst of war Hance recognised the importance of post-war reconstruction, and he was a member of the Bhore Commission on the health services of India He visited the United States to study American methods of medical education, and he returned to India to help to plan the Postgraduate Medical Institute at Delhi After his return to this country his work at the Commonwealth Relations Office was interrupted so that he could advise on the organisation of the health services of Ceylon under the Colombo plan Despite ill health he continued to work steadily and devotedly He died on Sept 5 at the end of an assignment abroad.

He was appointed C I E in 1939, promoted K C I E in 1946, and created K C.M G in 1953

G R McR writes

"Bennett Hance had a zest for life. He was ever vital and full of enthusiasm When I met him first in 1924 in Dera Ismail Khan he was experimenting with a new lamp which he had designed for carrying out blood-sugar estimation by McLean's method, and that only a few months after the introduction of insulin He had just finished a five-hour operation session I saw him again that evening, the floor of his living-room was covered with plans for new dispensaries in his wild remote frontier charge, his table with piles of figures for his annual drug and equipment estimates It was, I found, typical of the man—a day's work measured only by what could be squeezed into it He was an all-rounder, as ready to tackle a cholera epidemic as a Wertheim operation or an iridectomy His years in Persia provided him with a fund of Persian proverbs, which he quoted freely His service in Waziristan first brought him into contact with the wild Pathans, and he became a fluent speaker of Pushtu The Pathan servants whom he engaged there remained in his entourage throughout the rest of his service—strange and fearsome though they were among the gentler minions of Mysore.

"On his retirement from the post of director-general it was recognised that he had been one of the greatest holders of that post, for he had not only coped well with the great immediate problems of war-time India but had drawn up sound plans for reconstruction and progress in post-war independent India—plans which are working well today Over eleven years ago his left lung was removed for proved carcinoma Within three months he was back in harness, touring the world, planning, inspecting, and again planning As medical adviser in the Commonwealth Relations Office his dogged devotion to duty when hardly able to draw breath was marvelled at by all—he was always cheerful His end came suddenly and peacefully, on a brief holiday after an important mission oversea His brother officers will ever be grateful for the trouble he took over their resettlement hosts of students from oversea, patiently interviewed and placed by him for training under the Colombo plan, share that gratitude for the work of Bennett Hance"

By his first wife, Catherine, daughter of the late Dr C L Leonard of Philadelphia, Sir Bennett had two daughters In 1938 he married as his second wife Frau Richildis von Kaan, daughter of Richard von Warton of Vienna, who survives him

WILLIAM MOWLL FRAZER

O B E, M D, M Sc Lpool, D.P.H

Prof W. M Frazer, whose death on Sept. 8 we announced last week, was medical officer of health of the city and port of Liverpool from 1931 to 1953

He was born in 1888 in Liverpool and was educated at Liverpool and London Universities He took his M SC in 1909, but his medical studies were interrupted by the 1914–18 war, during which he served in the King's (Liverpool) Regiment Afterwards he returned to Liverpool University and qualified in 1921 The following year he took the D P H, for he had already chosen public health as his specialty He held appointments as assistant M O H at Blackburn, and as M O H at Dewsbury and Hull before he returned in 1931 to Liverpool as M O H Two years later he was appointed to the chair of public health at the University

His work in Liverpool centred round the city's hospital service, and it was largely thanks to him that at the outbreak of war in 1939 the Liverpool municipal hospitals were able not only to cope efficiently with the heavy civilian casualties of the city but also to help to care for the Service casualties who were brought to the port from overseas

For his work in Civil Defence he was appointed O B E in 1939, and during the war he was responsible for the Liverpool casualty services, together with the billeting services, which were sorely tried during the aerial bombardment of 1940 and 1941 He served on committees set up by the Ministry of Health and the Medical Research Council, and on the health committee of the Association of Municipal Corporations He gave the Chadwick and Newsholme lectures, and in 1942 visited the United States to lecture on public health at the request of the Ministry of Information. A prolific and gifted writer, he will be particularly remembered for his monograph *Duncan of Liverpool* (1947), his *Textbook of Public Health* (the earlier

Particulars, including diagrams, may be had from the general manager of British Legion Industries, Preston Hall, Maidstone, Kent

Royal College of Physicians of London

On Friday, Oct 17, at 3 P M , Sir Geoffrey Keynes will give the Harveian oration His subject will be Harvey through John Aubrey's eyes On Thursday, Nov 6, at 5 P M , Prof K W Donald will give the Bradshaw lecture on heart-disease and exercise On Tuesday, Nov 18, at 5 P M , Dr Mildred Creak will give the Charles West lecture The title of her lecture will be Child Health and Child Psychiatry—*Neighbours* or Colleagues? All the lectures will be given at the college, Pall Mall East, S W 1

Association of Clinical Pathologists

This association is holding a meeting from Oct 2 to 4, at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W C 2 To commemorate the centenary of the publication of Virchow's *Cellular Pathology* the meeting will include a symposium on the pathology of the cell The speakers will be Sir Roy Cameron, Dr Joseph Bamforth, Dr G R Osborn, Prof Robert Cruickshank, Dr Honor Fell, Prof N H Martin, and Dr A G E Pearse Further particulars may be had from Dr J N Cumings, The National Hospital, Queen Square, W C 1

M R C Travelling Fellowships

The Medical Research Council invites applications for travelling fellowships for 1959–60

These fellowships are intended for graduates resident in this country who have had some training in research in clinical medicine or surgery, or in some other branch of medical science, and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad, before taking up appointments for higher teaching or research in the United Kingdom Fellowships held in the United States will provide maintenance allowances, at rates varying from 3000 to 5000 dollars per annum, and travelling expenses Forms of application may be had from the secretary of the Council, 38, Old Queen Street, London, S W 1, and must be returned by Oct 31

British Postgraduate Medical Federation

The inaugural lecture of the 1958–59 series on the scientific basis of medicine will be given by Sir Edward Salisbury at 5 30 *P M on Thursday, Oct 16, at the Senate House, University* of London, Malet Street, W C 1 His subject will be the influence of botany on health and disease

Assessment and Education of Cerebral Palsied Children

The British Council for the Welfare of Spastics have arranged a conference on this subject for doctors on Saturday, Nov 8, at the Engineering School, University Walk, Bristol Prof A V Neale will be in the chair, and the speakers will include Dr R M Norman, Dr N S Alcock, Dr G E Woods, and Dr A L Smallwood Tickets (17*s* 6*d*) may be had from the secretary of the council, 13, Suffolk Street, Haymarket, London, S W 1

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Dr E H Hudson on Fridays, from Oct 3 to Dec 12 Open lectures will be given on Wednesdays, from Oct 1 to Dec 10, by Sir Russell Brock, Dr F P Lee Lander, Dr A B Paterson, Dr J R May, Dr F H Scadding, Dr Paul Wood, Dr A M C Macpherson, Mr V C Thompson, Dr N L Rusby, Mr W P Cleland, and Mr Donald Barlow All the meetings will be held at 5 P M , at the institute, Brompton Hospital, Fulham Road, S W 3

Inhaled Particles and Vapours

A symposium on this subject, arranged by the British Occupational Hygiene Society, will be held in Oxford in April, 1960 Further particulars may be had from Mr J S McLintock, Medical Service, National Coal Board, Hobart House, London, S W 1

Society of British Neurological Surgeons

On Wednesday, Oct 22, at 5 30 P M , at the London Hospital, Sir Geoffrey Jefferson will give the first Hugh Cairns memorial lecture He will speak on Sir Hugh Cairns Tickets may be had from Mr D W C Northfield at the London Hospital, E 1

Postgraduate Travelling Fellowships

The governing body of the British Postgraduate Medical Federation is offering a limited number of these fellowships to doctors and dentists Further particulars will be found in our advertisement columns

Medical Protection Society

The annual general meeting of this society will be held at Victory House, Leicester Square, London, W C 2, on Wednesday, Oct 1, at 3 P M

British Society of Dental Radiology

Representatives from the X-ray departments of dental schools and hospitals in the United Kingdom have formed this society under the chairmanship of Dr Sydney Blackman Further particulars may be had from Mr Guy Poyton, X-ray Department, Eastman Dental Hospital, Gray's Inn Road, London, W C 1

Royal Medico-Psychological Association

This association is holding a joint meeting with the Section of Psychiatry of the Royal Society of Medicine, at 1, Wimpole Street, London, W 1, on Thursday, Sept 25, at 5 P M , when Dr W E Barton, associate professor of psychiatry at Boston University, will speak on research in rehabilitation

Section of Psychotherapy and Social Psychiatry.—On Wednesday, Sept 24, at 8 P M , at 11, Chandos Street, W 1, Mr Richard Hauser will speak on community developments and group work in psychiatry

On Friday, Oct 10, at 5 P M , Mr William Doolin will give the opening sessional address of the Faculty of Medicine in the *Firth* Hall, University of Sheffield His subject will be *Is* History Bunk?

On Monday, Oct 6, at 3 P M , Sir Eric James, high master of Manchester Grammar School, will give the inaugural address of the new session to the faculty of medicine of the University of Birmingham, at Queen Elizabeth Hospital, Edgbaston, Birmingham

Postgraduate demonstrations in psychiatry will be held at St George's Hospital Medical School, Hyde Park Corner, London, S W 1, for doctors on alternate Thursdays from Oct 9 to Dec 4 at 5 P M Owing to rebuilding the demonstrations in neurology will not be resumed until the Lent term, 1959

Surgeon Rear-Admiral E T S Rudd has been appointed house governor and medical superintendent of King Edward VII Convalescent Home for Officers, Osborne, in succession to Sir Neil Cantlie

Lieut -Colonel C A Bozman, director of the Wellcome Museum of Medical Science, has been invited by the World *Health Organisation* to join a small team of consultants which is to *visit the* All India Institute of Public Health and Hygiene in Calcutta

Dr B Cinader has been appointed head of the subdivision of immunochemistry in the Ontario Cancer Institute and associate professor in the department of medical biophysics at the University of Toronto

Dr P W Hutton, *medical* specialist at Mulago Hospital, Kampala, Uganda, has been elected president of the Association of Physicians of East Africa

The address on Moral Responsibility in Clinical Research, by *Mr D MacG Jackson*, F R C S , which was summarised in our issue of April 26, has now been published in full for the Christian Medical Fellowship, by the Tyndale Press, 39, Bedford Square, London, W C 1 (pp 20 6*d*)

The annual students' dinner of University College Hospital Medical School *will be held at the* Savoy Hotel, Strand, London, W C 2, on Friday, Oct 24, at 8 P M Application for tickets (£1 12*s* 6*d*) should be made to the hon secretary *of the* students' association at the medical school Postgraduate *demonstrations* will be given at the school on Oct 23 and 24

The Lancet · Saturday 27 September 1958

ADRENALECTOMY IN CUSHING'S SYNDROME

MANAGEMENT AND METABOLIC ASPECTS

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Cushing's syndrome is a progressive fatal disease with an average duration of five years (Sprague 1953, Plotz et al 1952) The underlying metabolic disturbance is due to excessive secretion of adrenocortical hormones, but the anatomical lesion of the adrenal glands may be a tumour or bilateral hyperplasia Early attempts to control the activity of hyperplastic adrenals by resection proved disappointing

Cushing's syndrome was ameliorated but not abolished by the removal of one adrenal, and more extensive resection was too dangerous in the absence of adequate hormonal therapy (Cope and Raker 1955) However, the introduction of cortisone and hydrocortisone made it possible for patients to survive radical subtotal or even total adrenalectomy Many workers have recorded the abolition of Cushing's syndrome by the removal of at least 80% of adrenal tissue (Sprague 1953, Bishop et al 1954, Beck et al 1954, Coone and Humphreys 1956, Mason 1957) Hernberg (1954) suggested extensive subtotal resection of both adrenals Bishop et al (1954) and Montgomery and Wellbourn (1957) favour complete removal of one adrenal and, at a later date, resection of the remaining gland However, Poutasse and Higgins (1953) considered that both adrenals should be resected at one operation, and if the disease was severe no adrenal tissue should be left

We describe here our experience with adrenalectomy in the treatment of Cushing's syndrome associated with bilateral adrenal hyperplasia, and outline the therapeutic regime which we favour The data on serum-electrolytes and glucose tolerance are drawn from 17 patients with adrenal hyperplasia and 1 patient with Cushing's syndrome due to an adrenal carcinoma on whom special metabolic observations were made (case 1) Special metabolic studies, including nitrogen and potassium balances, were made before operation in 8 patients and after adrenalectomy in 9 instances

Diagnosis

Adrenalectomy, with its immediate dangers and prospect of permanent adrenal hypofunction, should be undertaken only when the diagnosis of Cushing's syndrome is proved beyond doubt First, difficulty may be encountered in adolescent girls who exhibit obesity, acne, pink striæ distensæ, menstrual irregularity, and even a slight rise in blood-pressure There may be some increase in the urinary metabolites of hydrocortisone, indicating hyperactive adrenal function, but the absence of muscle wasting and the presence of generalised obesity help to distinguish this from Cushing's syndrome It is essential to observe these patients, rather than to submit them to unnecessary operation, as the disturbance is transitory and responds to a reducing diet A similar type of benign transient disturbance is sometimes seen in young men In contrast to these conditions, which represent a minor deviation of endocrine physiology, is the adrenogenital syndrome in women, arising in puberty and continuing throughout life Such patients are plethoric, hirsute obese yet muscular, with irregular menstruation and, in later years, benign hypertension Urinary steroid excretion is increased, but this is mainly in the form of 17-ketosteroids However disfiguring the disease, it is not progressive or fatal, and therefore in our view adrenalectomy is seldom justified

The diagnosis of Cushing's syndrome requires investigation of both the disorder of function and the anatomical lesion The disturbance of physiology is apparent from the clinical features The effect of increased protein catabolism (or failure of anabolism) can be directly estimated by a nitrogen balance, but this is not essential Associated metabolic changes equally can be detected by the glucose-tolerance test and radiographic examination of bones (particularly the spine and ribs) for evidence of osteoporosis, spontaneous fracture of osteoporotic bone, especially in the ribs, is common Electrolyte disturbance must be investigated by estimation of serum sodium, chloride, potassium, and bicarbonate Because the electrolyte equilibrium is unstable in Cushing's syndrome, a single reading is unreliable and therefore serum-electrolytes should be measured on several occasions An electrocardiogram provides confirmatory evidence of potassium depletion The diagnostic significance of these metabolic changes will be discussed later

Hypertension is an important feature in prognosis, and requires careful assessment by repeated estimations of the blood-pressure with the patient at rest Full renal function tests, including estimations of blood-urea, creatinine clearance, and urinary urea concentration, should be carried out

Estimation of urinary 17-ketogenic steroids by the method of Norymberski et al (1953) has proved satisfactory, and by this method distinctly raised values were found in all our cases of Cushing's syndrome Nabarro et al (1957) were equally impressed by Norymberski's modified method (Appleby et al 1955) which measures 17-hydroxycorticosteroids Both these methods, however, measure other substances which are not derived from hydrocortisone, particularly steroids with 17 20-diol or 21-deoxyketol types of side chain which are excreted in large quantities in adrenal virilism Hence high values recorded by these methods are not specific for Cushing's syndrome The determination of 17-hydroxycorticoids by the Porter-Silber reaction, according to the method of Reddy et al (1952) does not have this disadvantage, but unfortunately it is less reliable than Norymberski's method (Moxham and Nabarro 1956) The excretion of 17-ketosteroids may be increased, decreased, or normal in Cushing's syndrome, so the level of these steroids is of no value in diagnosis (Butt et al 1950) Moreover excretion of all steroids is subject to considerable diurnal variation in Cushing's syndrome (Birke et al 1956), thus the estimation should be made in several (at least three) twenty-four-hour collections of urine

Anatomical diagnosis is more difficult and should be approached critically It is of advantage to determine the presence and location of an adrenal tumour, but it is not essential and X-ray methods such as presacral insufflation of air are neither completely reliable nor free of discomfort We do not think aortography is justifiable, it is difficult and unreliable in obese patients and may be dangerous In practice we have relied on straight X-ray examination and tomography, combined with intravenous pyelography to outline the position of the kidney A large proportion of tumours can be detected by this means

The final decision about the anatomical lesion is made at operation In hyperplasia both glands are enlarged (combined weights 10 2–26 1 g in this series) If a functioning tumour is present the opposite gland undergoes atrophy The type of lesion can therefore be determined when the first gland is exposed The appearance of a tumour is obvious on inspection If the gland is large, but no tumour is present, it can be assumed that hyperplasia is the cause, if it is small it must be left and the opposite side explored

Preoperative Metabolic Studies

Protein Catabolism

The clinical appearances of the patient are related to factors which may vary independently Thus severity of muscle wasting depends on duration rather than on the level of negative nitrogen balance For example, cases 8, 9, and 10 showed only moderate muscle wasting, and this was confirmed by levels of urinary creatinine within normal limits for their known weights before the onset of the disease Nevertheless, they showed a daily loss of nitrogen between 4 5 and 6 9 g with a normal protein intake, and in cases 8 and 10 the presence of creatinuria confirmed rapid muscle breakdown On the other hand, 1 patient (case 1), in whom Cushing's syndrome was due to an adrenal carcinoma, showed gross wasting and the level of creatinine output was roughly half the expected normal, nevertheless at the time of investigation she was losing only 1 4 g nitrogen daily In other cases the disease may be rapidly progressive in the absence of muscle wasting and without gross increase in protein catabolism, case 5, a girl aged 18, had florid Cushing's syndrome with severe hypertension, yet the mean daily nitrogen loss was only 0 4 g

Repletion of protein stores and stimulation of anabolism is extremely difficult in the presence of Cushing's syndrome The results of high-protein feeding are disappointing, even though the nitrogen balance may become positive at first Thus in case 1 muscle wasting was severe, and nitrogen equilibrium was achieved on a diet containing 56 g of protein , When protein intake was increased to 105 g daily there was a positive balance of 3 1 g of nitrogen daily from the fourth to the eighth day, but from the fourteenth to the eighteenth day she retained only 0 6 g nitrogen daily

We have no data on the effect of high-fat diets in Cushing's disease, but studies were made in a patient with Cushing's syndrome after massive cortisone therapy A daily intake of 140 g had no " sparing " effect on protein catabolism, and the daily nitrogen loss was increased by 1 2 g

Potassium supplements have been shown by Albright (1942) to diminish nitrogen loss in patients with potassium depletion In 1 patient in this series (case 1), increasing the potassium intake to 200 mEq daily was followed by a decrease in urinary nitrogen of 1 3 g daily In another patient (case 5) a moderate increase of potassium intake from 60 to 90 mEq daily was sufficient to correct potassium depletion (as indicated by serum level) and urinary nitrogen fell to 0 5 g daily These results indicate that high potassium intake diminishes nitrogen loss, but this is incidental to the potassium repletion and is not otherwise of value in countering protein breakdown

The known action of testosterone in promoting anabolism led Albright et al (1941) to investigate its value in Cushing's syndrome, and it was found to produce significant nitrogen retention We have studied the effect of testosterone propionate on 1 patient (case 9) in different states of nitrogen balance Before operation he was in negative balance of 4 5 g nitrogen daily Intramuscular testosterone 25 mg daily for five days reduced this to 2 06 g , but it was not possible to reverse the negative balance After adrenalectomy the patient was in positive balance and the same course of testosterone increased this by 2 56 g daily—i e , the anabolic effect was quantitatively similar whether the patient was initially in positive or in negative nitrogen balance The expected potassium retention corresponding to the nitrogen retention during these two periods of testosterone administration should be 6 6 and 6 9 mEq daily The observed diminution in urinary potassium during the two periods was 6 6 and 9 3 mEq respectively, the serum-potassium remaining constant

TABLE I—PREOPERATIVE METABOLIC DATA

Case no	Study	Days of collection	Balance (mean daily)		Glucose-tolerance test blood-sugar (mg per 100 ml)			Remarks
			N (g)	K (mEq)	Fasting	¾ hr *	2 hr *	
1	Untreated	4	−1 4	+15		Diabetic		Serum-K 2 3 mEq per litre
	High K intake	5	−0 1	+80				Serum-K rose to 3 1 mEq per litre
	High protein							
	4th–7th day	4	+3 1					
	14th–17th day	4	+0 6					
5	Untreated	6	−0 4	+3	70	146	150	Serum-K 3 6 mEq per litre
	High K intake	8	+0 11	+20				Serum-K rose to 4 35 mEq per litre
8	Untreated	5	−6 9	−8	66	128	72	Studied during relapse serum-K normal
9	Untreated	5	−4 53	+17	90	124	150	
	Testosterone	5	−2 06	+23				Serum-K normal
	4th week after adrenalectomy	5	+4 24	+19				
	Testosterone	5	+6 31	+28				
10	Untreated	4	−5 2	+3	84	130	102	Serum-K normal
14	"	3	+1 5	—	104	200	132	Serum-K normal
16	"	2	+1 7	−2	80	132	132	Serum-K normal
17	High K, high protein diet, and insulin	4	−5	+30		Diabetic		Serum-K 4 7 mEq per litre Had risen from 3 1 mEq after 3 weeks on high K diet High protein diet only for one week

* After 50 g glucose by mouth

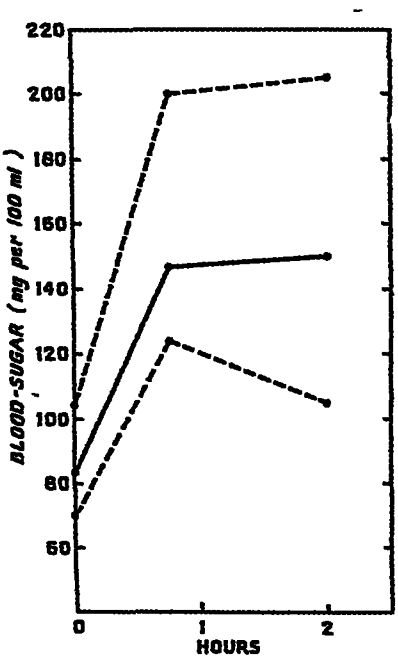

Fig 1—Glucose tolerance in 10 cases with impaired tolerance continuous line mean, interrupted lines, maximum and minimum blood-sugar levels.

Impaired sugar tolerance is a characteristic feature of Cushing's syndrome, and its assessment has some value in diagnosis It is in part related to the degree of increased protein catabolism and in part to the antagonism between hydrocortisone and insulin In this series abnormal glucose-tolerance curves were obtained in 13 of the 18 patients (In case 8 the curve was abnormal before his initial operation, but normal during the relapse of Cushing's syndrome two years later) 3 were typical diabetic curves—1 in the case of adrenal carcinoma (case 1) and 2 in patients with adrenal hyperplasia (cases 3 and 17) The mean curve for the remainder is shown in fig 1 There was no consistent relationship between the degree of decreased carbohydrate tolerance and negative nitrogen balance—which indicates that antagonism between hydrocortisone and insulin is chiefly accountable for the diabetic behaviour in Cushing's syndrome.

Electrolyte Disturbances

Disturbances in electrolyte balance in Cushing's syndrome were first reported by McQuarrie et al (1937) Teabeaut et al (1950) and Sprague et al (1950) noted hypokalæmia with hypochloræmic alkalosis, usually associated with adrenal carcinoma Such a finding is rare in Cushing's syndrome, and in this series was observed only once (table II, case 1) In this patient the serum-potassium was 2 3 mEq per litre, serum-sodium 139 mEq per litre, serum-chloride 86 mEq per litre, and serum-bicarbonate 41 mEq per litre, at operation an adrenal carcinoma was found. Gross muscle weakness was present, and this was abolished when the serum-potassium rose to 3 1 mEq per litre following high potassium intake During the phase of severe hypokalæmia the patient was in positive balance, as in the case recorded by Teabeaut et al (1950) The degree of potassium loss was not related to nitrogen loss, which was only slight Furthermore, although a positive potassium balance was quickly obtained, complete repletion proved difficult since the urinary output of potassium rose following increased intake This would be expected if the potassium loss were due to excessive production of mineralocorticoids—not necessarily due to aldosterone, as Garrod and Tait (1957) found no increase in urinary aldosterone in their cases of Cushing's syndrome with hypokalæmia

TABLE II—PREOPERATIVE SERUM-ELECTROLYTES (MEQ PER LITRE) (ABNORMAL FIGURES)

Case no	Sodium	Chloride	Potassium	Bicarbonate
1	139	*86*	*2 3*	*41*
4	*162*	*108*	4·0	30
5	137	105	*3 6*	30
6	140	*109*	*3 3*	30
7	*152*	*112*	4 1	
9	*150*	101	4 8	31
11	*156*	95	5·0	29
12	*163*	*110*	*3 5*	
17	143	95	*3 1*	32

Abnormal readings in italics.

Lesser degrees of potassium depletion were found in 4 of 15 patients with Cushing's syndrome due to adrenal hyperplasia (table II), and again there was no correlation between the rate of protein catabolism and potassium depletion (table I) The serum-potassium levels were below 4 0 mEq per litre, but there was no fall in serum-chloride or rise in serum-bicarbonate. Case 5 was in potassium equilibrium when the serum-potassium was 3 6 mEq Complete and sustained potassium repletion was obtained by increasing the intake by 30 mEq daily The cumulative balance over fourteen days showed a retention of 181 mEq of potassium (the serum level rising from 3 6 to 4 35 mEq per litre) and 53 mEq of sodium, and a loss of 137 mEq of chloride This indicates a loss of intracellular chloride as cellular potassium is restored It is apparent that hypochloræmic alkalosis is a late result of potassium deficiency and that in the earlier stages we find only a lowered serum-potassium Moreover, potassium replenishment is achieved easily when the serum chloride and bicarbonate are normal, but with considerable difficulty at the stage of hypochloræmia In either case, correction of potassium deficiency is an essential preliminary to operation

An abnormally high serum-sodium level was found in 5 of the 15 cases, and, of these, chloride was increased in 3 and potassium was decreased in 1 (table II) This hypertonicity of the serum was probably due to sodium retention Pitting œdema was present in 1 patient, but water retention did not usually balance sodium retention 1 patient (case 10) was studied over a period of seven days during which there was a loss of 4 lb in body-weight and 107 mEq of sodium, yet the serum-sodium rose from 150 to 162 mEq per litre Although salt retention, being less severe, has not the practical importance of potassium depletion, this aspect of Cushing's syndrome should not be neglected

TABLE III—TOTAL NITROGEN LOSS AND TOTAL CREATININE EXCRETION IN SEVEN DAYS AFTER ADRENALECTOMY

Case no	Creatinine (g)	Nitrogen (g)
8b	13 73	50·4
8a	12 23	55 2
10	9 89	89 3
16	7·05	27 26
15	6 16	39 8
14	5 01	28·02
17	4 71	12 8
1	3 77	0

Treatment

Selection of Cases and Operation

We have selected for operation only those patients in whom the diagnosis of Cushing's syndrome was beyond doubt and the disease was definitely progressive Assessment of rate of progress has been based on clinical features such as hypertension, muscle wasting, and weakness, together with the data obtained from metabolic studies of protein catabolism and electrolyte disturbances

Previous work (Sprague et al 1950) showed that at least 75% of hyperplastic adrenal tissue must be removed in order to reverse the metabolic disorder in Cushing's

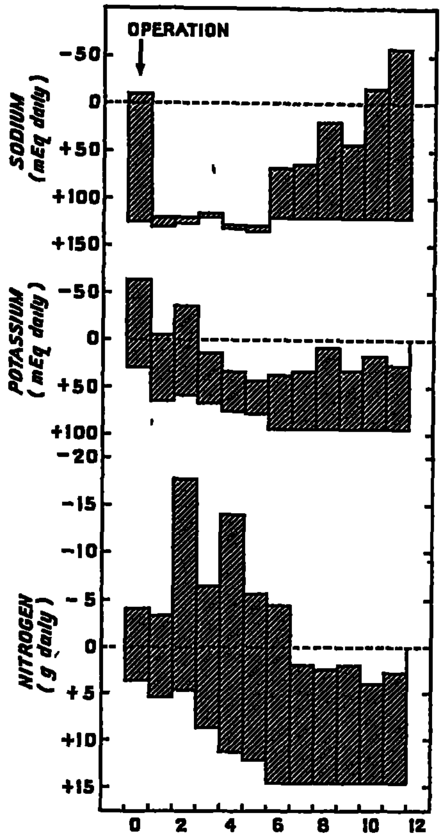

Fig 2—Balance data, case 8a

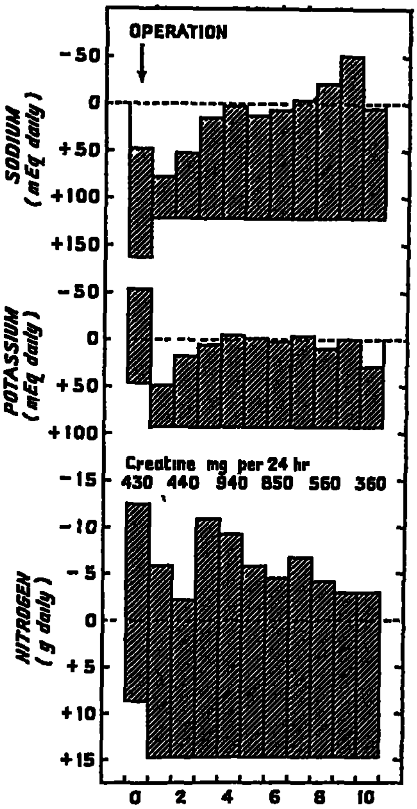

Fig 3—Balance data, case 8b

syndrome There is, however, a very narrow margin between removing enough adrenal tissue to prevent relapse and so much that adrenal hypofunction results In patients under 25 years, and in rapidly progressive, very severe Cushing's syndrome at any age, there is for practical purposes no margin and total adrenalectomy is the operation of choice (Mason 1957) In patients over 45 years, with a more slowly progressive disease, relapse is less likely and subtotal adrenalectomy, leaving only 20–25% of the adrenal tissue, is both adequate and safer

These patients are more likely to suffer from hypertensive vascular disease, which is unlikely to be relieved by the operation and adds to the surgical risk Removal of the adrenals by two operations is often advocated (Bishop et al 1954, Montgomery and Welbourn 1957), and we would endorse this view as regards older patients—especially those with evidence of hypertensive vascular disease In younger patients, however, we feel that, with adequate preparation, the immediate surgical risks of bilateral adrenalectomy in a single operation are less than in two operations, largely owing to the greater hazard of postoperative chest complications associated with two operations

Preoperative Medication

This is needed, first, to correct the existing metabolic disturbance and, second, to cover the sudden deprivation of cortical steroids by adrenalectomy In the rare cases with a diabetic sugar-tolerance curve, insulin will be required The main preoperative therapy is, however, adequate cortisone administration This must be sufficient to maintain the excessive level of circulating glucocorticoids to which the patient has become accustomed, and after operation the dose must be adjusted so that reduction to normal levels is gradual and controlled The dosage scheme is the same for total or subtotal adrenalectomy in a single operation, but differs when the procedure is carried out in two stages In the single-stage operation the dosage of cortisone is far higher than that required for removal of normal adrenals (Mason 1955) and varies according to the degree of preoperative adrenal hyperfunction The following dosage schedule has been found suitable for a one stage adrenalectomy in patients with active progressive Cushing's syndrome

	mg daily
For two days before operation	150
Day of operation and subsequent two days	300
Fourth and fifth day after operation	200
Sixth day after operation	150
Seventh day after operation	100

Cortisone then to be given orally (four doses per day) and reduced every other day to maintenance levels (25–50 mg daily)

Cortisone was not given orally over the immediate period of the operation, because of the

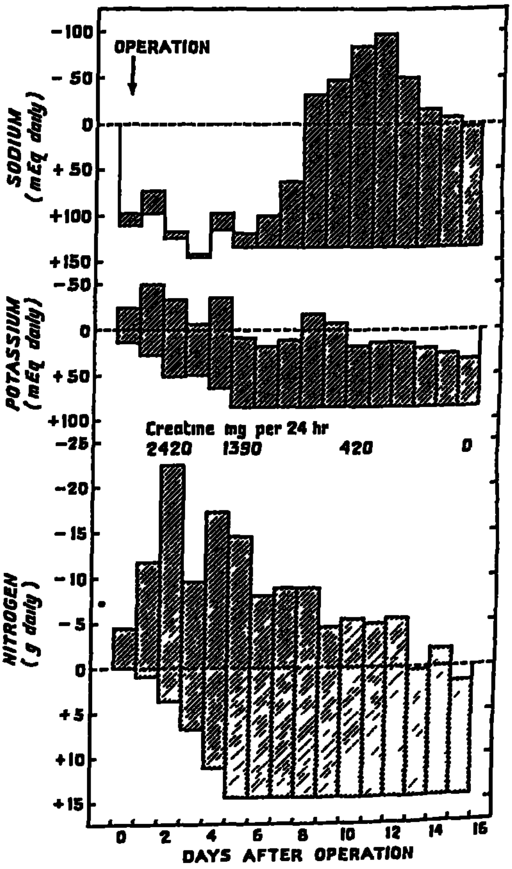

Fig 4—Balance data, case 10

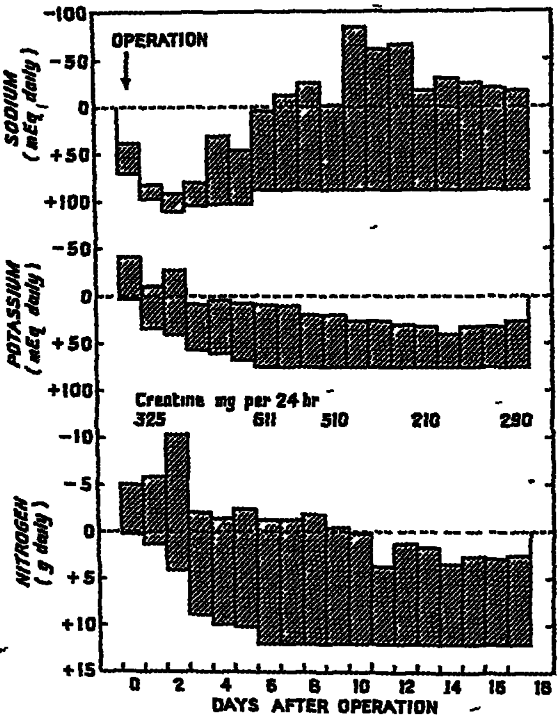

Fig 5—Balance data, case 14.

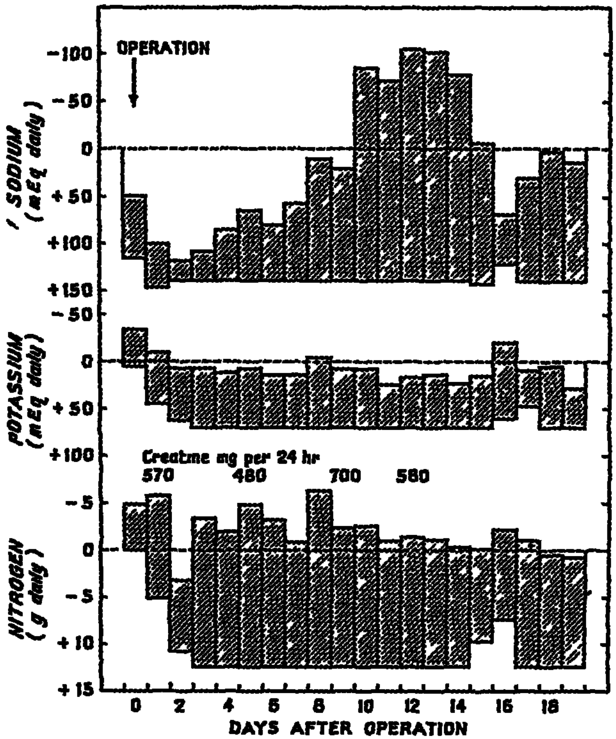

Fig 7—Balance data, case 16

dangers of vomiting and defective absorption Intramuscular injections were given twice daily, starting at least forty-eight hours before operation to ensure adequate absorption Postoperatively the injections were replaced by oral cortisone only when gastrointestinal function had returned to normal

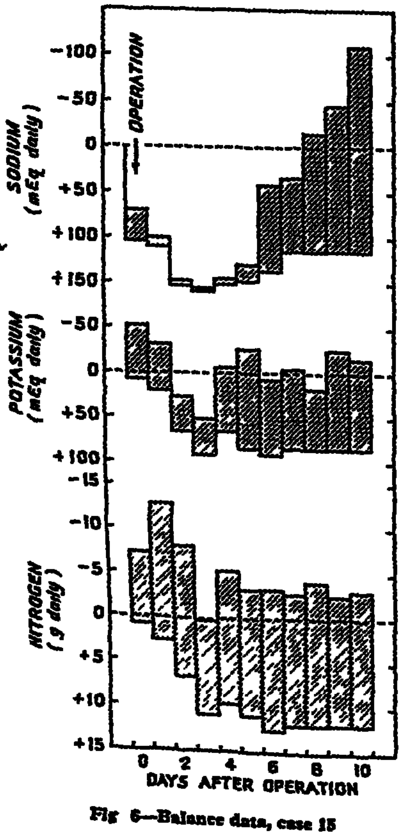

Fig 6—Balance data, case 15

No evidence of postoperative adrenal insufficiency has appeared in patients treated with the above regime Substitution therapy with cortisone alone is sufficient, and the balance data recorded below confirm that there is no need for addition of a mineralocorticoid such as deoxycortone acetate or fluorohydrocortisone in the early postoperative phase

Operative Details

Whether total or subtotal adrenalectomy is to be performed the right adrenal is first removed complete The subcutaneous tissues and muscles are infiltrated with 120 ml of 0 3% lignocaine with 0 5 ml *1 in 1000 adrenaline on each side* If the hypertension is severe the adrenaline is omitted The 11th rib is resected, the diaphragm is divided, and the peritoneum is freely opened The kidney is pushed down and the lung upwards On the right side the liver must be pushed up, and on the left the spleen and pancreas *displaced medially* after division of the peritoneum between spleen and diaphragm On the right the inferior vena cava is located, and then the medial border of the adrenal gland, the wide short vein thus exposed between the two is divided. Sometimes the adrenal is wrapped round and extends behind the vena cava, this part must be dissected, and then the rest from medial to lateral In this way the most difficult part of the dissection is done in a dry field The wound is closed in layers without drainage.

If subtotal adrenalectomy is to be done the whole of the left adrenal is displayed after removing the right An incision is made at a level which would leave $^1/_8$–$^1/_{10}$ of the gland, according to its size If the medial cut surface bleeds and retains its normal colour, its blood-supply is presumed to be adequate and the lateral portion is removed. Biopsy specimens are taken from both kidneys to assess the extent of renal vascular damage

When the patient is turned after the first side is completed, shock may develop even though blood loss has been slight This is due to loss of vasomotor tone in the anæsthetised patient, leading to pooling of blood on the dependent side A blood-transfusion must therefore be started at the end of the operation on the first side

Subtotal resection of each adrenal is in our view inadvisable since, if relapse occurs it is impossible to decide which side should be re-explored. Complete removal of the right adrenal is preferable since hypertrophy of a remnant is more difficult to deal with on this side owing to proximity to the vena cava

Postoperative Care and Complications

On return from the theatre the patient is nursed with blocks to the foot of the bed These are removed when consciousness returns Over the next twelve hours the patient is gradually raised, according to the level of the blood-pressure, to a sitting position An intravenous infusion of 4% glucose and $N/5$ saline is kept running in case noradrenaline or hydrocortisone is needed, and to provide the necessary fluid and electrolytes Intramuscular cortisone is continued according to the regime already described Oral administration of water, electrolytes, or hormones is to be avoided owing to the common development of abdominal distension, presumably as a form of ileus, due partly to the retroperitoneal dissection and partly to the pre-existing metabolic disturbance Gastric aspiration, intravenous fluids, and electrolytes, analgesics, and sedatives may be required until normal gastro-intestinal function is restored During the first few post-operative days fluid intake should not exceed the urine volume plus 1 5–2 0 litres for insensible loss, and not more than 140 mEq sodium daily should be given Larger amounts are harmful and may prolong the ileus Intravenous administration of potassium seems unnecessary

Acute adrenal insufficiency is the earliest and most serious complication We have not observed this since the adoption of the cortisone dosage described above Before this, however, 1 fatal case occurred

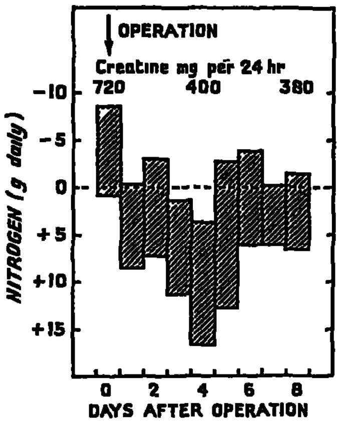

Fig 8—Balance data, case 17

Case 6, a girl aged 16 years, had a severe, rapidly progressive Cushing's syndrome Bilateral subtotal resection of the adrenals was carried out leaving approximately $^1/_{10}$ of each gland There was no incident in her progress until eleven hours after her return to the ward, when she collapsed with a rapidly rising pulse-rate and, rather later, a severe fall in blood-pressure Electrocardiography revealed sinus tachycardia with no evidence of electrolyte imbalance The pulse-rate remained at 160, and the blood-pressure was unrecordable The extremities were extremely cold and pale, there was no respiratory difficulty and no abnormal signs were found in the chest She was mentally alert and very apprehensive, and complained of weakness, vomiting and nausea were absent Her condition remained virtually unchanged until death twenty-eight hours after operation Necropsy revealed bilateral thrombosis of the adrenal remnants but gave no definite indication of the cause of death In this case 75 mg cortisone had been administered intramuscularly daily for two days, and a further 150 mg was injected three hours before adrenalectomy After operation a further dose of 150 mg was injected soon after she collapsed The total water intake, mainly intravenous, was 5 litres in the twenty-four hours after operation, the urine volume over this period was 1 litre Intravenous noradrenaline was given in an attempt to raise the blood-pressure, but despite continued and increasing dosage had no significant effect

Subsequent experience and the reports of other observers clearly indicate that this syndrome is due to inadequate cortisone therapy before and immediately after operation A possible contributory factor was the excessive water intake The failure of noradrenaline to raise the blood-pressure in these circumstances has been noted by others, and the correct emergency treatment is now known to be continuous intravenous administration of hydrocortisone hemisuccinate 50 mg initially followed by 10 mg per hour This is a most effective treatment for acute adrenal insufficiency, and should always be immediately available for patients undergoing adrenalectomy

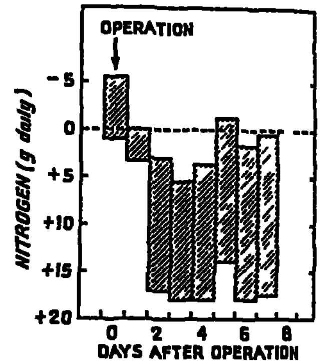

Fig 9—Balance data, case 1

In addition to this acute form of cortical insufficiency, symptoms may arise more insidiously owing to a too rapid fall in circulating corticoids at any time after operation This is particularly likely to occur after radical subtotal adrenalectomy, if the adrenal remnant produces insufficient hormone when cortisone is withdrawn Similar symptoms occur during convalescence if the dosage of cortisone is lowered too rapidly The symptoms include complete anorexia, lethargy, arthralgia, mental depression, irritability, and withdrawal from contact with others (Sprague 1953, Cope and Raker 1955) Electrolyte changes are absent, the pulse-rate seldom rises significantly, and the blood-pressure is maintained, indeed the hypertension of Cushing's syndrome may persist Prompt increase in the dose of cortisone immediately relieves the symptoms

Pulmonary complications are next in severity It is most important at the end of the operation to expand the lungs fully to minimise this risk Hæmothorax and pneumothorax occurred in 2 patients, but responded to appropriate treatment, with complete re-expansion of the lung In 1 patient infection developed in the left subphrenic space, this drained spontaneously and the sinus took a considerable time to heal There is a definite risk of fatal pulmonary emboli (Mason 1957) in those patients who

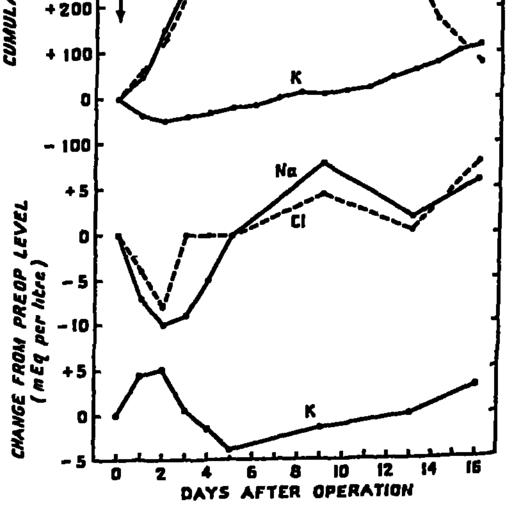

Fig 10—Post-adrenalectomy changes in plasma-electrolytes case 16

are weak and heavy, with a sluggish peripheral circulation and a tendency to bruise easily. Owing to abdominal distension and a liability to postural hypotension adequate postoperative movement is difficult to achieve. 3 patients in this series had a non-fatal pulmonary embolus.

In 1 patient (case 13) the hæmoglobin fell steadily by about 10% each day for five days. After blood-transfusion her hæmoglobin rose and did not fall again. There was no clinical evidence of bleeding in the pleural or peritoneal cavities or of gastrointestinal hæmorrhage, and chest X-ray showed no abnormality. This phenomenon was never explained.

In this series of 17 cases there have been 2 deaths, the 1st (described above) due to acute adrenal insufficiency and the 2nd, in a patient aged 54, due to a combination of hypertensive heart-failure and respiratory failure associated with postoperative pulmonary collapse (case 17). This 2nd case illustrated the operative risk in an elderly patient with poor respiratory and cardiac reserve.

Postoperative Metabolic Studies

Information on the metabolic changes after bilateral adrenalectomy in Cushing's syndrome is scanty. As this has a considerable bearing on treatment, postoperative balance studies were made on 7 patients in this series. (Case 8 was studied twice: (a) at initial operation, (b) at second operation on account of relapse after eighteen months.) The results are illustrated graphically in figs 2–9. The direction and duration of changes in nitrogen, potassium, and sodium balance are similar to those found after any form of operation or trauma (Moore and Ball 1952). In 3 instances (cases 8a and b and 10) nitrogen loss was heavy, and in all it was maximal at the first to third day after operation; positive nitrogen balance was usually achieved by the seventh to twelfth day. Another patient (case 9, table I) showed a strongly positive nitrogen balance several weeks after operation. The degree of nitrogen loss was not directly related to the dosage of cortisone, but was greater than that observed after the removal of normal adrenals (A. S. Mason, unpublished). This is to be expected since the preoperative level of protein catabolism was raised in these patients. There was a rough parallelism between the degree of nitrogen loss and the postoperative output of creatinine, which may be taken as a guide to the lean body mass. Thus case 1 (with adrenal carcinoma) and case 17, who were both grossly wasted and had a subnormal creatinine excretion, showed a very slight postoperative loss of nitrogen.

This increased protein catabolism after operation is qualitatively the same as normal protein breakdown—i.e., 90% of urinary nitrogen is in the form of urea. There was, however, an increase in urinary creatine in the 5 cases in which this was measured after operation compared with preoperative levels. Case 10, with the most negative nitrogen balance, had the highest creatine excretion over a twenty-four-hour period (2.42 g., fig. 4), and in others creatinuria was proportional to the degree of nitrogen loss (see table III). This finding presumably indicates a rapid postoperative breakdown of muscle tissue; a similar but smaller degree of creatinuria occurs after other operations—i.e., this is not specific for adrenalectomy in Cushing's syndrome.

Postoperative potassium loss was slight and a positive balance was achieved after the first three days. Serum-potassium levels remained normal throughout, but usually rose slightly in the first three days after operation.

Changes in sodium and chloride were greater; retention of these persisted until the seventh to the tenth day after operation, when diuresis occurred. During the first forty-eight to seventy-two hours after operation water was retained in excess of sodium; the consequent fall in serum-sodium level was from 6 to 9 mEq. per litre in 7 cases. A typical curve is shown in fig. 10. Nevertheless all these patients were in positive sodium balance. Thus case 15 retained 70 mEq. of sodium in the first twenty-four hours after operation, but the serum level dropped by 6 mEq. per litre. Case 10 retained 431 mEq. of sodium in the first four days after operation, and the serum level fell by 9 mEq. per litre. Sodium retention continued for some days after water excretion returned to normal, so the serum concentration was restored to preoperative levels or above by the fifth or sixth day after operation.

Certain practical conclusions can be drawn from these results. Firstly, measurement of serum levels gives no accurate indication of electrolyte balance. Secondly, there is no need to administer additional mineralocorticoids (such as deoxycortone) over the immediate period of operation. Thirdly, the daily intake of sodium, either intravenously or by mouth, should not exceed 140 mEq. daily. Lastly, the amount of water given intravenously and by mouth during the first two to three days after operation should not exceed the urine volume by more than 1–1.5 litres daily.

These observations apply only to the initial phase of sodium and water retention. In the later period of convalescence the patient requires a high salt intake if electrolyte balance is to be maintained with cortisone therapy. Some patients will undoubtedly require not only cortisone but the continued administration of a mineralocorticoid; fluorohydrocortisone is the most suitable hormone for oral therapy.

Summary

Preoperative and postoperative studies have been made in 17 patients with Cushing's syndrome associated with bilateral adrenal hyperplasia, and in 1 case of adrenal carcinoma. The following conclusions have been reached.

(1) The diagnosis and the progressiveness of the disease must be established beyond doubt before surgery is undertaken.

(2) Both the disturbance of physiology and the anatomical lesion must be considered. There are at present no adequate methods of restoring protein. The electrolyte disturbance must be corrected before operation.

(3) In the younger patients and in those with rapidly progressive disease total adrenalectomy is recommended. In older patients subtotal adrenalectomy is preferred. In the younger patients the operation is carried out in one stage and in older patients in two stages.

(4) The most important item in the immediate preparation for surgery is administration of sufficient cortisone to maintain the excessive level of glucocorticoids to which the patient has become accustomed. To ensure absorption over the time of operation and during the postoperative period the cortisone must be given intramuscularly. Intake of water and sodium must be limited in the immediate postoperative period. The dose of cortisone must be gradually reduced, and later the amount of salt increased.

(5) The most serious postoperative complication is acute adrenal failure. It should be treated by hydrocortisone hemisuccinate, which should always be available in case of emergency. The other complications are ileus, pulmonary embolism, hæmothorax, and pneumothorax.

We are grateful to the physicians of the hospital who have sent us patients, and especially to Prof. Clifford Wilson who has also given us advice in the preparation of this paper, to Mrs. Scott, sister in

charge of the metabolic wards, who did so much to help us with these studies, and to Mr G C Tresidder who operated on one of the cases and has permitted us to refer to this patient

REFERENCES

Albright, F (1942) *Harvey Lect* 38, 123
— Parson, W , Bloomberg, E (1941) *J clin Endocrin* 1, 375
Appleby, J I , Gibson, G , Norymberski, J K , Stubbs, R D (1955) *Biochem J* 60, 453
Beck, R N , Montgomery, D A D , Welbourn, R B (1954) *Lancet*, ii, 1140
Birke, G , Plantin, L O , Diczfalusy, E (1956) *J clin Endocrin* 16, 286
Bishop P M F , Glover, F N , De Mowbray, R R , Thorne, M G (1954) *Lancet*, ii, 1137
Butt, W R , Mason, A S , Morris, C J O R (1950) *ibid* ii, 894
Coone, H W , Humphreys, J W (1956) *Ann intern Med* 44, 188
Cope, O , Raker, J W (1955) *New Engl J Med* 253, 119, 165
Garrod, O , Tait, J F (1957) *Proc R Soc Med* 50, 770
Hernberg, C A (1954) *Acta endocr , Kbh* 16, 309
Mason, A S (1955) *Lancet*, ii, 632
— (1957) *Proc R Soc Med* 50, 766
McQuarrie, I , Johnson, R M , Ziegler, M R (1937) *Endocrinology*, 21, 762
Montgomery, D A D , Welbourn, R B (1957) *Brit J Surg* 45, 137
Moore, F D , Ball, M R (1952) Metabolic Response to Surgery Springfield, Ill
Moxham, A , Nabarro, J D N (1956) *J clin Path* 9, 351
Nabarro, J D N , Moxham, A , Walker, G (1957) *Brit med J* ii, 1018
Norymberski, J K , Stubbs, R D , West, H F (1953) *Lancet*, i, 1276
Plotz, C M , Knowlton, A I , Ragan, C (1952) *Amer J Med* 13, 597
Poutasse, E F , Higgins, C C (1953) *J Urol*, 70, 129
Reddy, W J , Jenkins, D , Thorn, G W (1952) *Metabolism*, 1, 511
Sprague, R G (1953) *Proc R Soc Med* 46, 1070
— Hayles, A B , Power, M H , Mason, H L , Bennett, W A (1950) *J clin Endocrin* 10, 289
Teabeaut, R , Engel, F L , Taylor, H (1950) *ibid* p 399

MALIGNANT DISEASE OF THE URINARY TRACT *

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MALIGNANT growths of the kidney and ureter account for only about 2% of all malignant tumours, yet their clinical presentation is so variable that they often present a difficult diagnostic problem Nevertheless this problem can be solved with almost complete certainty if the right investigations are done These growths show in a striking manner that duplicity which we have come to associate with cancer of the urinary tract whilst some are highly lethal, others follow a relatively benign course The outcome in an individual patient, however, can be foretold with some confidence when all the facts are known

THE KIDNEY

In a nation-wide survey of over 2000 cases collected for the British Association of Urological Surgeons in 1951 parenchymal tumours accounted for about 75% and tumours of the pelvis for about 12% of renal cancers The remainder included some of the most interesting rarities of surgical practice, as well as the Wilms tumours in children My personal series includes 142 cases (table I) The adult parenchymal tumours are solid adenocarcinomas arising in renal epithelial cells they are better known as Grawitz tumours, or by the now discredited name of hypernephromata The pelvic tumours can be either papillary, like similar tumours in the bladder, or solid and either transitional- or squamous-cell

TABLE I—MALIGNANT DISEASE OF THE KIDNEY

Parenchymal carcinoma		89
Secondary carcinoma		1
Sarcoma		1
Pelvic tumour	Epithelial	43
	Sarcoma	1
Tuberous sclerosis		1
Wilms tumours		6
Total		142

Pathology

Whilst there is no proof that a benign renal adenoma can become malignant, there is considerable probability that it does so (Newcomb 1937, Thackray 1953) The possibility of a hormonal factor in the ætiology is suggested by the 2-to-1 preponderance of males over females, chronic simple infection and stone-formation appear to have an influence on the production of the uncommon squamous cell carcinoma of the renal pelvis Papillary tumours of the pelvis may also result from the excretion of carcinogens, but, unless there is unilateral hydronephrosis, this explanation hardly accounts for their usual one-sided distribution

Renal tumours can spread by direct extension and by the lymphatics, but they endanger life chiefly by their predilection for invading venous radicles, the renal vein, and the inferior vena cava

The particular tendency of papillary tumours of the pelvis is to spread to other parts of the urinary tract by the urogenous dissemination either of cells or of a carcinogenic agent

Clinical Features

In a disease with such wide pathological variations it is to be expected that the clinical manifestations will also differ from patient to patient It becomes all the more important to pick out the cardinal symptoms and signs In renal neoplasms there is a classical triad—hæmaturia, pain, and tumour These may be late in appearance, and they may not all be present in any one case, but in most patients they give the first evidence of the disease

Intermittent fever occurs in some cases of both parenchymal and pelvic growth (Griffiths and Thackray 1949, Rowlands 1951) Without necrosis it may be an anaphylactic manifestation (Wright 1922), but, whatever its cause, in my experience it indicates a bad prognosis Loss of weight and anæmia may occur, as in any malignant condition Varicocele on the right side should still be regarded with suspicion, despite the rarity of one which disappears after right nephrectomy

The primary lesion in the kidney may not declare itself until it erodes a calyx or until it attains a large size Before this it has sometimes invaded a vein, and it may have given rise to distant metastases or, quite often, to a solitary deposit

Of skeletal sites the spine heads the list, and sudden paraplegia may be the first indication of renal neoplasm A deposit in a long bone may appear as a pulsating swelling, with the radiographic picture of bone destruction, it can be a teasing examination problem In the lungs the metastases are generally multiple, but solitary tumours have been excised and palpable enlarged lymph-nodes in the neck are sometimes found at an early stage

In at least 4 known cases priapism from a deposit in the penis was the presenting symptom There is, in fact, scarcely a part of the body, including the skin, the thyroid, and the testis, in which a metastasis has not been the first indication of a renal tumour, and because such secondary tumours are so often solitary, their excision may be the proper procedure

The incidence of such a presentation was given as 50%, by Israel in 1896 and as 9% by Deuticke in 1931, but in our series in 1951 it was only 3 2% Such is the effect of modern methods of investigation

The true silent tumours are those which are discovered at necropsy, or when operating for some other condition, such as stone I have seven of these on record

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* Based on the third Lettsomian lecture for 1958, delivered before the Medical Society of London

Diagnosis

The aim of diagnosis is not limited to the finding of an neoplasm in the kidney It should disclose whether the growth is parenchymal or pelvic, because the treatment of the two differs, and it should determine its operability and the presence of complications It may also give some idea of the prognosis

An opportunity to perform cystoscopy whilst bleeding continues should be seized gratefully If blood is seen coming only from one ureteric orifice the site of bleeding is at once determined. The decoy prostate is eliminated, and that refuge of the destitute, varicose veins in the bladder, is no longer needed

Excretion pyelography is always very informative and, if there has been no opportunity for cystoscopy during bleeding it should be the first major investigation Retrograde pyelography is essential if there is no excretion or poor definition on the intravenous pyelogram In any event it will give a good idea of the extent of the filling defect, and it should serve to distinguish a parenchymal from a pelvic growth.

Aortography

Despite the clear picture it gives, a retrograde pyelogram shows only that there is a space-filling lesion In practice this may be a tumour or a cyst, and, although the diagnosis can often be inferred from the clinical features, the distinction can generally be made by aortography—which is not such a terrible investigation as some seem to think

A parenchymal tumour is vascular the vessels are displaced, and there is usually an irregular deposit of contrast medium in the venous spaces of the growth which gives it a mottled appearance This is known as "pooling" By contrast, a cyst is avascular it shows as a clear area in the nephrogram Pelvic papillary tumours show no specific signs on aortography Solid pelvic tumours are avascular, a pelvic tumour which invades the parenchyma may give rise to an avascular defect in the nephrogram, as may a parenchymal tumour which invades the pelvis

Perhaps the greatest value of aortography will prove to be in the detection of an early carcinoma when the pyelogram is equivocal or the ureter cannot be catheterised We have thus diagnosed a tumour only 15 mm in diameter

Perirenal Oxygen Insufflation

Although rarely needed in the diagnosis of renal tumours, the injection of oxygen by the presacral route can show whether the growth is fixed to its surroundings This may determine the degree of operability and the need for preoperative irradiation.

Treatment and Prognosis

There is general agreement, at least among surgeons, that the treatment of carcinoma of the kidney is nephrectomy with early ligation of the renal vein and removal of the perinephric fat. It is also accepted that in papillary tumours of the pelvis the ureter should be removed with the kidney There is some difference of opinion on the value and place of irradiation in treating kidney cancer A study of the survival-rates has a bearing on these matters (Priestley 1939, Griffiths and Thackray 1949, Riches, Griffiths, and Thackray 1951) it shows that, whilst some of these growths are rapidly fatal, others progress slowly We have tried to analyse the various factors which influence the prognosis in the individual case

1 Histological Grade

The grading is similar to that described for bladder tumours it is based solely on the microscopic appearance The objection has been raised that areas of different grades may be found in the same growth; but just as one bad link weakens a chain, so one area of high malignancy condemns the whole tumour

Of 80 tumours removed by nephrectomy 39 were grade-1, 25 were grade-2, and 16 were grade-3 There were 6 operative deaths 8 further cases were deemed inoperable, and in a fit lady of eighty-seven, with a three-year history of hæmaturia suggestive of a slowly growing tumour, I decided not to operate

TABLE II—5-YEAR SURVIVAL OF PATIENTS OPERATED ON BEFORE JANUARY, 1953

—	Number of cases	Survivals
Total	59	29 (49%)
Grade 1	27	18 (67%)
Grade 2	19	8 (42%)
Grade 3	13	3 (23%)

Table II shows that a rising scale of histological malignancy is reflected in a lower survival-rate. A similar conclusion was reached in 100 patients in the B.A.U.S. series, and Thackray (1957) has shown more recently the same correlation in patients followed for ten years

2 Involvement of the Renal Vein

Macroscopic invasion of the renal vein was seen in 13% of low-grade and 44% of high-grade tumours in this series It can generally be recognised at the time of operation, and an attempt should be made to tie the vein beyond the malignant thrombus It reduces the five-year survival for all grades from 49 to 28%

3 Invasion of the Lymph-nodes

Invasion of lymph-nodes occurred in 6 patients in equal proportions in the three grades 2 lived for about seven years, 1 for four, and 1 for three years Although survival is shortened, these glands respond well to postoperative irradiation If possible, they should be removed with the kidney Excision of recurrent invaded glands in the neck is also worth while. Ultimately 5 of the 6 cases developed other metastases

4 Local Extension

Local infiltration of the perinephric fat, muscles, the colon, the pancreas, or other viscera had taken place in 23% of my cases It was more frequent in growths of high-grade malignancy Its effect on survival is serious, but it does sometimes respond to irradiation.

5 The Presence of Metastases

The existence of metastases is not always a contraindication to nephrectomy This may be required for the relief of pain, hæmaturia, or pyrexia, or on the assumption that removal of the primary growth is likely to make irradiation of the secondary more effective

Metastases were present at the time of the nephrectomy in 9% of my patients Separate excision of a metastasis from the chest wall was possible in 1 patient only, but he is alive nearly five years later Others have had relief from X-ray therapy My figures are insufficient to show whether metastases are commoner with high-grade growth, but I believe that they are It is certain that grade-3 metastases grow more quickly and destroy life earlier

6 The Method of Treatment

So long as the surgical treatment is radical enough, any approach which gives a wide exposure may be adopted

I prefer generally to work through the bed of the excised twelfth or eleventh rib, conversion to the Nagamatsu incision is possible if required. I do not find it easier to secure the renal vein earlier by the abdominal route this is so by the abdominothoracic exposure, but a kidney which can only be removed in this way may not be worth removal In the

B A U S series there was a higher operative mortality after the abdominal than after the lumbar incision

The use of X-ray therapy is controversial There is no doubt that some renal carcinomas are radiosensitive, and there is enough evidence to show that the more anaplastic ones are the more responsive In the larger series (1951) the addition of postoperative conventional X-ray therapy improved the results in all cases, but survival figures were improved most in those, largely of high-grade malignancy, in which the vein was involved Since then I have made it the rule to advise postoperative X-ray therapy for most patients, excluding only those with small tumours of low malignancy, very fat patients, and those who cannot take it The certain indications for it are tumours of high malignancy, venous involvement, lymph-node invasion, or local extension

In a small but increasing number of patients preoperative X-ray treatment has also been given, and study of such patients, known to me personally, has been instructive Some, who would be expected to do badly, have done well

A woman of forty-nine had a tumour which appeared both clinically and on perirenal oxygen insufflation to be fixed After X-ray treatment it became smaller and more mobile, and the oxygen passed around its upper pole The kidney was removed without difficulty though it was a grade-2 growth and the vein was invaded she is alive and well six and a half years later

A man of forty-seven was found at operation elsewhere to have a fixed, irremovable kidney the wound was closed and he was given X-ray therapy I then exposed the kidney again, divided some dense scar tissue, and removed it This was also a grade-2 growth with the vein invaded, but he is alive and well eleven years later

A man of fifty-five had hæmoptysis A shadow near the sixth rib posteriorly was suspected as a carcinoma of the bronchus, but investigations at a chest hospital proved negative A year later he had hæmaturia, and we found a right renal tumour The thoracic shadow was now clearly a destructive palpable metastasis in the ribs He was given conventional X-ray therapy to the rib area and treatment on the linear accelerator to the kidney I then did a nephrectomy The kidney was adherent and on section necrotic, but it was a low-grade tumour with the vein free The lesion in the ribs has shown a progressive diminution in size and apparent calcification in its outline, it is no longer palpable and he is very well at the end of a year

In view of such cases I feel that more use should be made of preoperative radiotherapy, especially if supervoltage machines are available The diagnosis must be certain and aortography may be necessary to make it so If the histological grade or the state of the vein could be known before operation the choice would be easier, but I do not think that renal biopsy is justified for this purpose

I have no doubt that the histological grade of the tumour is the most important single factor in prognosis High-grade malignancy is beyond our control but it may prove possible to mitigate its effects by supervoltage therapy This is our present plan There are of course exceptions to every rule, in this series they are 3 survivors of fifteen years, thirteen years, and eight years, all with anaplastic tumours None had irradiation The vital factor of individual resistance will always have the last word in the argument

RENAL PELVIS AND URETER

The widespread involvement of the urinary tract by papillary tumours is shown by the distribution of the 43 cases in this series (table III)

TABLE III—SPREAD OF 43 EPITHELIAL TUMOURS OF THE RENAL PELVIS AND URETER

Distribution	No
Pelvis alone	15
Ureter alone	4
Pelvis and bladder	9
Ureter and bladder	3
Pelvis and ureter	3
Pelvis, ureter, and bladder	9

These tumours are composed of transitional or squamous epithelium with a few mixed forms Clinically the important division is into the papillary and the less common solid type their behaviour resembles that of the papillary and solid growths of the bladder respectively The squamous-cell tumours are all solid

6 papillary transitional-cell tumours which were histologically benign are included in the series 2 of them affected more than one part of the urinary tract though benign tumours show a higher survival-rate than those described as transitional-cell carcinomas, they have the same age-incidence and the same tendency to spread

Treatment

The treatment of pelvic papillary tumours is nephro-ureterectomy Dealing with the intramural part of the ureter some patients have had a disc of bladder excised, and some, following the advice of Macalpine (1947), have had this part treated by cystoscopic diathermy after section of the ureter flush with the bladder Coexisting or recurrent growths in the bladder have been controlled by cystodiathermy, but 2 patients needed total cystectomy and ureterectomy after the kidney had been removed elsewhere I believe that the kidney tumour usually precedes those in the bladder, and recognition of the renal origin of these bladder growths is essential On the other hand, they may appear in a bladder previously clear as long as two years after nephrectomy and ureterectomy and failure to remove the ureter may result in tumour appearance in the stump What is perhaps most important in the removal of these growths is the avoidance of spill, either of urine or of tumour-cells

A few of the pelvic tumours are radiosensitive In one man with a fixed, inoperable anaplastic growth the mass became smaller, the affected kidney regained some function, and subsequent inguinal metastases disappeared with radiotherapy He died after two years from pulmonary metastases

Dr Thackray classifies pelvic papillary tumours into low and high grades

The 10 patients who lived for five years all had tumours of low-grade malignancy Some have not been available for grading, but out of 18 known low-grade tumours 10 (55%) lived for five years and 4 died earlier from other causes 7 had recurrence or metastasis Of 5 patients with known high-grade growths 1 lived for three years and 1 for two, but none of the others passed the six-month mark 4 of the 5 had recurrence or metastases

Although a widespread distribution of these papillary growths affects survival adversely, it is not so important a factor as the grade of malignancy Low-grade tumours gave rise to metastases in the lungs or liver only after long survival, although local recurrence was more frequent In high-grade tumours bloodborne metastasis was more frequent than local recurrence The solid transitional-cell tumours are much more malignant no patient lived for a year after operation, and metastases in the lungs, brain, skin, or lymph-nodes appeared in 5 out of 7 Radiotherapy did not seem to help them

Squamous-cell *growths were too few to analyse, but they* are known to have a poor prognosis

WILMS TUMOUR (NEPHROBLASTOMA)

That infants and young children can be afflicted by malignant disease of the kidney is one of the cruelties of Nature That it should be of such intense malignancy as is found in Wilms tumour is a refinement of cruelty

In the B A U S series (1951) there were 189 cases of nephroblastoma of which half had occurred between the ages of two and four years Only 8 had been in children under one year, an important fact since it has been shown that the prognosis is better in younger children Boys and girls are affected equally Hæmaturia, which indicates extension to the pelvis, is of bad prognostic import, it occurred in 18% of the patients The renal vein was involved in 8%

Many of these tumours shrink under the influence of radiotherapy, but Higgins and his colleagues (1951) think that these are of higher malignancy and always recur Preoperative *irradiation has a debilitating effect*, and the best reason for its use is to make a very large tumour smaller and easier to remove Gross (1953) used it in alternate cases for a year, but he found that the mortality " skyrocketed "

Early nephrectomy without unnecessary manipulation is indicated It should be followed by postoperative irradiation, starting as soon as possible after operation

Many observers think that survival of eighteen months to two years implies cure, but metastases have been found as late as five years after nephrectomy and local recurrence after eight years In the 189 cases we collected the three-year survival was 26%

The most informative figures are those of the Boston workers (Gross and Neuhauser 1950) They are given in table IV

TABLE IV—" CURE " RATE OF CASES WITH WILMS TUMOUR (GROSS AND NEUHAUSER)

—		Patients under 1 yr	Patients over 1 yr	All ages
Period A	1914–30 27 cases (4 cures)	42 8%	5%	14 9%
Period B	1931–39 31 cases (10 cures)	71 4%	20 8%	32 2%
Period C	1940–47 38 cases (18 cures)	80%	43 3%	47 3%

In period A nephrectomy alone was used.
In period B the transperitoneal route was the rule, but anæsthesia and preoperative and postoperative care had improved greatly
In period C postoperative X-ray treatment was added
The term " cure " indicates a two-year survival free from recurrence.

In a few cases, 3 6% according to Scott (1956), the condition is bilateral

CONCLUSIONS

I hope it is evident that throughout the urinary tract there are two main types of malignant disease Results of treatment cannot be compared without saying whether the tumours were solid or papillary, and whether they were anaplastic or differentiated There will also be some which were intermediate

Though this general survey is based on personal experience, it must be obvious that I owe a great debt to my teams of assistants throughout the years My colleagues have collaborated generously, and I owe especial thanks to Prof B W. Windeyer, to Dr A. C. Thackray, and to Dr C G Whiteside Mr Cowan, the records officer, has checked my figures and made the tables *I must finally express my deep gratitude to* my former chief, Sir Gordon Gordon-Taylor, for stimulating my interest in the surgery of malignant disease

REFERENCES

Deutcke, P (1931) *Dtsch Z Chir* 231, 767
Griffiths, I H , Thackray, A C (1949) *Brit J Urol* 21, 128
Gross, R E (1953) The Surgery of Infancy and Childhood, p 588 Philadelphia
— Neuhauser, E B D (1950) *Pediatrics*, 6, 843
Higgins, T T , Williams, D I , Nash, D F E (1951) The Urology of Childhood, chapter 13, p 208 London.
Israel, J (1896) *Dtsch med Wschr* 22, 345
Macalpine, J B (1947) *Brit J Surg* 35, 113
Newcomb, W D (1937) *Proc R Soc Med* 30, 113
Priestley, J T (1939) *J Amer med Ass* 113, 902
Riches, E W , Griffiths, I H , Thackray, A. C (1951) *Brit J Urol* 23, 297 (The B A.U S series)
Rowlands, B C (1951) *ibid*, p 267
Scott, L S (1956) *Brit med J* i, 200
Thackray, A C (1953) *in* Modern Trends in Urology (edited by E W Riches), chapter 12, p 117 London
— (1957) *Proc R Soc Med* 50, 362
Wright, H W S (1922) *Brit J Surg* 9, 383

INTRA-ARTICULAR THERAPY IN RHEUMATOID ARTHRITIS

COMPARISON OF HYDROCORTISONE TERTIARY BUTYL ACETATE AND HYDROCORTISONE ACETATE

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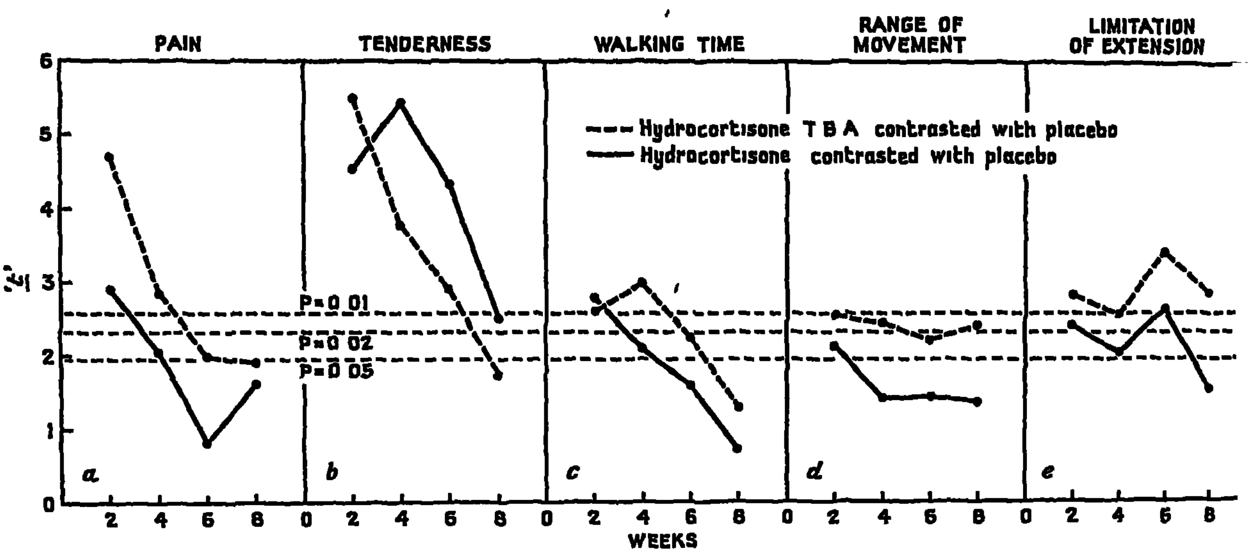
THE intra-articular injection of hydrocortisone acetate, introduced by Hollander et al (1951), is generally regarded as of value in the treatment of rheumatoid arthritis Most patients derive subjective benefit but the effect is usually transient In 1955 a less soluble ester, hydrocortisone tertiary butyl acetate (T B A.), was developed for intra-articular therapy with the claim that its anti-inflammatory effects were more pronounced and of longer duration Hollander et al (1955) found that of 92 patients with rheumatoid arthritis, 62 experienced greater relief and 49 longer benefit from hydrocortisone T B A than from hydrocortisone Duff (1956) stated that of the different chemical forms of local hydrocortisone the T B A preparation was probably the most effective Contradictory results were reported by Zuckner et al (1956), who found no difference in antirheumatic response between the two compounds None of these studies were made in strictly controlled conditions We report here the results obtained by a double-blind crossover trial designed to evaluate these drugs Each patient received both compounds as well as placebo and thus served as his own control

Design of Trial

The clinical material comprised 24 patients with rheumatoid arthritis whose principal disability arose from involvement of the knees In 13 both knees were treated, giving a total of 37 joints suitable for trial on the evidence of active inflammatory changes No patient was accepted whose treatment within the previous two months had included systemic or intra-articular steroid therapy, symptomatic treatment remained constant throughout the period of study which was conducted under outpatient conditions



Comparison of effects of hydrocortisone T B A and hydrocortisone Horizontal axis shows *four* two-week periods after each course treatment Vertical axis shows significance of difference between means of each measurement (t)

a, Effect on pain Significant improvement lasted *four* weeks *after* hydrocortisone T B A and two weeks after hydrocortisone

b, Effect on tenderness Significant improvement lasted six weeks after hydrocortisone and hydrocortisone T B A

c, Effect on walking time Significant improvement lasted four weeks after hydrocortisone T B A and two weeks after hydrocortisone

d, Effect on range of movement Probably significant improvement lasted eight weeks after hydrocortisone T B A compared with on barely significant improvement for two weeks after hydrocortisone

e, Effect on limitation of extension Significant improvement lasted eight weeks after hydrocortisone T B A, and 6 weeks after hydrocortison

The trial consisted of three courses (hydrocortisone, hydrocortisone T B A, and placebo) each of four fortnightly injections, with eight weeks' rest between treatments Dosages of hydrocortisone T B A and hydrocortisone were 25 mg (1 ml) Placebo (1 ml) was the vehicle used as the suspending and preserving agent for the T B A compound The order of courses in each patient was randomised from a master sheet on which names were entered consecutively Injections were given by one of us (G N C) and assessments made every two weeks throughout both the injection and rest periods by the same physician (V W) The nature of the injections was unknown both to the patient and to the assessor

The fortnightly assessments comprised measurements of erythrocyte-sedimentation rate (E S R) walking time over 75 yards, range of joint movement and limitation of extension determined by a goniometer (judgment of joint movement by eye must introduce an important source of error and should be abandoned in favour of more accurate measurement), tenderness (graded 0 = none, 1 = slight, 2 = definite, 3 = patient winces, 4 = withdrawal and/or exclamation), pain (graded 0 = none, 1 = slight on walking, 2 = pronounced on walking, 3 = pain at rest, 4 = severe pain at rest)

Radiographs of the knees were obtained before and after the trial

Results

6 patients failed to complete the trial 1 defaulted after the second course of injections, 4 required admission to hospital after two courses had been given because of deterioration of arthritis, and 1 developed unrelated disease soon after the trial began Withdrawals were scattered evenly throughout the random groups

The specific data (walking time, &c) derived from the first assessment in each treatment period were compared with the same measurements made at the four assessments in the succeeding eight-week rest period Changes in pain and tenderness were evaluated from difference in grading, changes in walking time and joint movement were estimated as a percentage of the pre-treatment measurements, change in limitation of extension w recorded as a percentage of maximal joint range (145° In this way the effect of treatment, both immediate an sustained, was calculated for each of the three treat ments in every patient The mean change for eac group (hydrocortisone, hydrocortisone T B A, and placebo between pre-treatment assessments and each of the fou post-treatment assessments was analysed by conventiona statistical methods (difference of means of unpaire data)

Pain

Significant relief of pain lasted four weeks in patient who had received hydrocortisone T B A, compared wit two weeks in patients who had received hydrocortison (fig *a*) Though greater relief was experienced fro hydrocortisone T B A than from hydrocortisone th difference was not significant at any assessment

Tenderness

Significant improvement in joint tenderness laste six weeks with both drugs Probably significant improvement was still present at the eighth week after hydrocortisone (fig *b*) The difference between the two drug was not significant

Walking Time

Significant benefit lasted four weeks after hydrocortisone T B A, compared with two weeks after hydrocortisone (fig *c*) Except at the first assessment, improvement was greater in patients who received hydrocortisone T B A but the difference between the two treatments was not significant

Range of Movement

Probably significant improvement lasted eight weeks after treatment with hydrocortisone T B A Improvement from hydrocortisone was barely significant at the second week and thereafter became insignificant (fig *d*) There was no significant difference between the two drugs

Limitation of Extension

Significant improvement lasted eight weeks after hydrocortisone T B A compared with six weeks after hydrocortisone (fig 6) There was no significant difference between the two drugs

E S R

There was no significant change in E S R as a result of treatment Throughout the period of study there was a gradual rise in mean E S R which was unaffected by the order in which treatments were given.

Subjective Assessment

The 18 patients who completed the trial were asked to state which course of injections had helped them most 6 preferred hydrocortisone T B A, 4 placebo, and 1 hydrocortisone 7 ranked hydrocortisone T B A and hydrocortisone equal and preferred these to placebo

Complications

2 patients experienced local exacerbation of arthritis, lasting one and three days, after injections of hydrocortisone T.B A 3 patients developed deep-vein thrombosis in the injected leg (2 after hydrocortisone and 1 after placebo)

Discussion

This trial was planned to assess the comparative value of hydrocortisone acetate and hydrocortisone T B A in the local treatment of rheumatoid arthritis Improvement from treatment was measured by fortnightly assessments of pain, tenderness, walking time, range of movement, and limitation of extension On these criteria both drugs showed a significant advantage over placebo Except in the case of joint tenderness, hydrocortisone T B A gave greater improvement which was of longer duration than that from hydrocortisone, but the difference between the effect of the two drugs was not significant in any instance It is possible, but unlikely, that larger numbers might show a more definite benefit that would support the claims made for the greater effectiveness of hydrocortisone T B.A Hydrocortisone had a slight advantage over the T B.A preparation in relief of joint tenderness, but this also was not significant. The random order in which the three courses of injections were given neutralised the expected advantage of first treatment and could not be held to account for the differences observed

There was no consistent or significant change in E S R that could be ascribed to the effect of any particular treatment, so local improvement was presumably independent of any systemic action No important side-effects were encountered apart from transitory post-injection exacerbation of symptoms in 2 patients after injection of hydrocortisone T B.A

The conflicting claims made for the relative effectiveness of intra-articular injections of hydrocortisone and hydrocortisone T B A (Hollander et al 1955, Duff 1956, Zuckner et al 1956) almost certainly reflect failure to conduct trials under controlled conditions Fearnley et al (1956) described a pilot study of intra-articular procaine and hydrocortisone acetate in rheumatoid arthritis which explored the possibilities of a crossover design for evaluating differences between drugs Similar methods, with the additional advantage of a double-blind procedure, have been used in this investigation Such conditions are an essential prerequisite for the proper assessment of treatment in a disease where bias and chance have so commonly led to favourable reports on remedies now discarded

Summary

The effects of intra-articular injections of hydrocortisone acetate and hydrocortisone tertiary butyl acetate (T B A) have been studied in 24 patients with rheumatoid arthritis whose main incapacity arose from involvement of the knees

Each patient was given three courses of injections (hydrocortisone, hydrocortisone T B A, and placebo) in random order Each course consisted of four injections at fortnightly intervals, with eight weeks' rest between courses Pain, tenderness, walking time, range of joint movement, and limitation of extension were assessed every two weeks Neither the patient nor the assessor was aware of the nature of the injections in any course

Both drugs showed a significant advantage over placebo Improvement was generally greater and of longer duration with hydrocortisone T B A. than with hydrocortisone, but the difference was not statistically significant

We are indebted to Messrs Merck, Sharp & Dohme for a generous supply of hydrocortisone T B A We are grateful to Sister P R Benson and her nursing staff for their cooperation

REFERENCES

Duff, I F (1956) *Postgrad Med* 19, 577
Fearnley, G R., Lackner, R, Meanock, R I, Bywaters, E G L (1956) *Ann rheum Dis* 15, 134
Hollander, J L, Brown, E M, Jessar, R A, Brown, C Y (1951) *J Amer med Ass* 147, 1629
— — — Udell, L, Smuckler, N M., Bowie, M A (1955) *ibid* 158, 476
Zuckner, J, Machek, O, Ahern, A M (1956) *Ann rheum Dis* 15, 258

DELETERIOUS EFFECT OF INTRA-ARTICULAR HYDROCORTISONE

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IN a controlled trial of intra-articular steroid therapy in rheumatoid arthritis, both hydrocortisone acetate and hydrocortisone tertiary butyl acetate (T B A) were found to give significant clinical improvement lasting several weeks (Chandler et al 1958a) Four injections of each drug and four of placebo were given into the knees over a period of forty-eight weeks during which physical grading and functional capacity were measured every fortnight Both drugs showed a significant advantage over placebo, but we were disturbed to find that, despite the generally good clinical response to injections of hydrocortisone and hydrocortisone T B A, radiological deterioration, sometimes considerable, had occurred in the knees of over half of patients so treated We report here the radiological findings and consider the possible mechanism by which deterioration occurs

Investigation

Radiographs of the knees (anteroposterior and lateral) were obtained before and after treatment in the 18 patients who completed the trial Twenty-five joints were injected and the X-ray appearances graded into five categories of severity for each feature of the rheumatoid

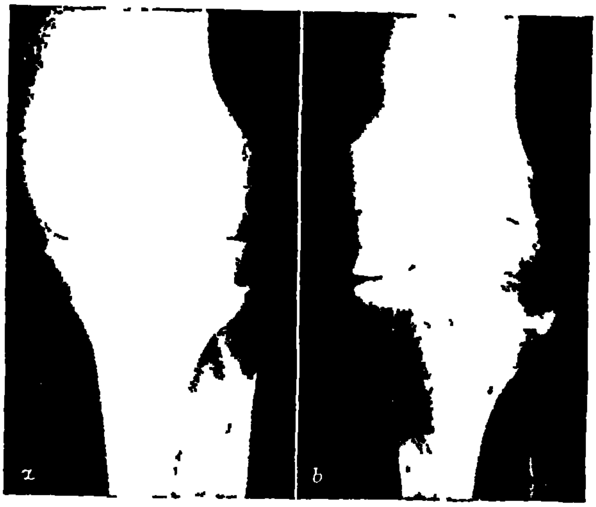

Fig 1—Case 5: Radiographs of left knee (*a*) before and (*b*) after treatment Second radiograph shows distinct increase of joint damage by erosion, and further loss of joint space

process (porosis, lost of joint space, and erosions), together with an overall rating as suggested by Kellgren and Lawrence (1957) 13 joints—just over half—showed radiographic deterioration Definite worsening occurred in 8, distinct deterioration in 3, and severe deterioration in 2 (table I)

Examples of deterioration are shown in figs 1 and 2

The data were then analysed to determine whether any correlation existed between the clinical response to treatment and radiological deterioration The changes in the initial and final clinical assessments of joint conditions were graded into three categories—improved, unchanged, worse—and considered in relation to radiological change

TABLE I—RADIOGRAPHIC FINDINGS IN 18 CASES BEFORE AND AFTER TREATMENT

Case no	Joint	Grade before treatment				Grade after treatment				Deterioration
		Porosis	Joint space	Erosion	Overall grading	Porosis	Joint space	Erosion	Overall grading	
1	L	2	1	0	1	2	1	2	2	+
2	R L	1 1	1 2	1 1	1 1	1 1	2 2	2 2	2 2	+ +
3	L	1	2	2	2	3	2	3	3	+
4	R	3	2	2	2	2	2	2	2	0
5	R L	2 1	4 3	4 1	4 2	3 4	4 3	4 4	4 4	0 +++
6	R L	3 3	2 2	1 0	2 2	3 3	2 2	1 0	2 2	0 0
7	R	1	2	2	2	2	2	2	2	0
9	R	1	0	0	0	1	0	0	0	0
10	R L	2 1	3 2	1 0	2 1	2 2	3 2	2 1	3 2	++ +
11	R	3	2	2	2	2	3	3	3	++
14	R L	2 2	1 2	1 2	1 2	2 2	2 2	2 2	2 2	+ 0
15	R	2	0	1	1	2	0	2	2	+
16	L	2	0	0	1	2	0	0	1	0
17	R L	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
19	R	2	2	2	2	2	2	3	3	+
20	R L	1 2	2 2	1 1	1 1	3 3	2 2	4 3	3 3	+++ ++
23	L	3	3	4	4	3	3	4	4	0
24	L	2	0	2	2	0	0	2	2	0

Grading of radiographic changes 0=normal, 1=doubtful, 2=minimal, 3=moderate 4=severe.
Deterioration in joint condition 0=none, +=definite worsening, ++=much deterioration, +++=gross deterioration

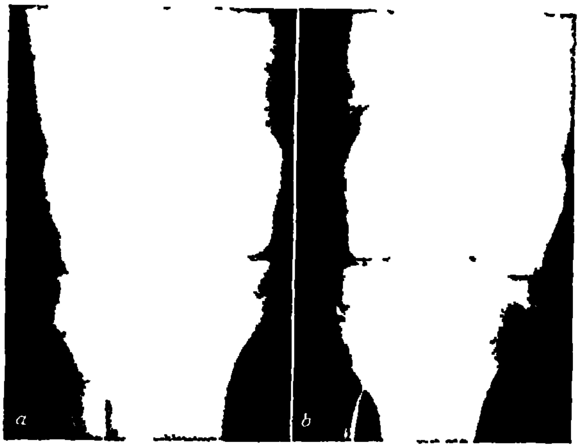

Fig 2—Case 20 Radiographs of right knee (*a*) before and (*b*) after treatment Second radiograph shows further notable increase in joint damage by erosion

Fig 3 shows that, as might be expected, the group of patients without radiological deterioration contained a larger number of good responses (10 out of 12 joints) than the group in which deterioration had occurred (7 out of 13) The difference was not important (χ^2=·80, P=0·4) and indicated that there was no significant association between overall clinical response and radiological change In each radiological group 1 patient deteriorated clinically

The three most useful measurements of joint function (pain, walking time, range of movement) were considered separately in relation to radiological change Immediate and sustained improvement in clinical status after each course of treatment with hydrocortisone and hydrocortisone T B A were estimated at the second and sixth weeks Mean improvement in pain was calculated from the difference in grading, mean improvements of walking time and range of movement were estimated as a percentage of pre-treatment measurements Since the curve of improvement in these criteria of joint function followed the same pattern after both treatments the data deriving from the effect of each were considered together in relation to radiological change (table II)

There was no significant difference in the amount of improvement of pain and range of movement between the group of patients in whom radiological deterioration occurred and the group in whom no such change was observed At the second and sixth weeks after treatment relief of pain was greater in the group who showed radiological deterioration, but the difference was not significant Only in respect of walking time was a significant difference apparent A tendency at the second week to greater improvement in the group with radiological deterioration became definitely significant at the sixth week (P=0·01) Range of movement showed greater improvement in the group without radiological worsening of disease, though this was not significant

Discussion

Undoubtedly the intra-articular injection of hydrocortisone and hydrocortisone T B A into the knees of patients with rheumatoid arthritis leads to clinical im-

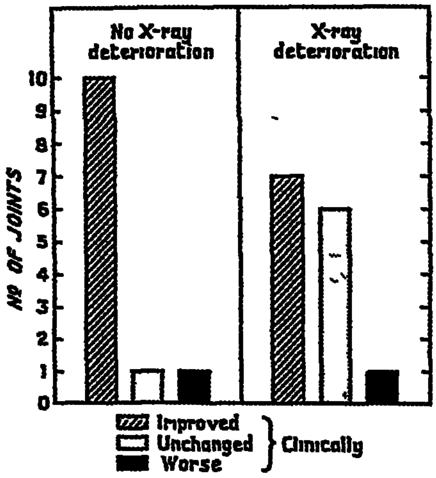

Fig 3—Relation of clinical response to radiological change.

provement which is encouraging to the physician and appreciated by the patient. Nevertheless in this series of patients who took part in a controlled trial of these compounds radiological deterioration, often considerable, was observed in over half This disturbing and unexpected finding could be held to result from inevitable progression of disease, but two pieces of evidence are contrary to such an interpretation First, the group of patients who showed unmistakable and often severe radiological deterioration on the whole fared only slightly less well, judged by clinical criteria, than the group in whom no advance in the radiographic features of arthritis occurred Secondly, the experience in the Empire Rheumatism Council (1955) trial of aspirin and cortisone in rheumatoid arthritis was that radiological deterioration in the large joints did not occur in a year's observation, with scarcely an exception radiological changes were limited to the small joints of the extremities The implications from the present study are definite Intrasynovial injections of hydrocortisone and related compounds either failed to halt or, more usually, accelerated pathological changes, despite the clinical relief enjoyed by the majority of patients

This apparent paradox of worsening disease in the face of clinical improvement was subjected to further investigation by analysis of the data derived from the various clinical assessments of joint function. No significant association could be traced between the effects of treatment on pain and range of movement in the two groups of patients with and without radiological progression of arthritis An important difference between the groups was, however, apparent in respect of walking time, a trend towards greater improvement at the second week after treatment in the group with deterioration became very significant at the sixth week It must be concluded that the principal effect of treatment in this group has been the attainment of a standard performance beyond the capacity of the joint. The discrepancy between the effects on pain and walking time in the two groups is probably more apparent than real Walking time is to be preferred as a measurement of improvement, for the quantification of pain is notoriously imprecise The fact that it was not until the sixth week after treatment that improvement of walking time became significant in the group with radiological deterioration suggests that sustained relief rather than immediate improvement is the damaging factor

TABLE II—EFFECT OF TREATMENT ON JOINT FUNCTION RELATED TO RADIOGRAPHIC CHANGE

Factor	Weeks after treatment	Mean improvement		Standard error of difference of means	P
		Group with X-ray deterioration	Group without X-ray deterioration		
Pain*	2	1·52	1·29	±0·38	<0·6
	6	0·88	0·67	±0·37	<0·6
Walking time†	2	7·0	4·7	±2·43	<0·4
	6	8·5	0·2	±3·1	<0·01‡
Range of movement	2	7·7	8·5	±2·96	<0·8
	6	6·1	6·6	±3·09	<0·9

* Improvement in pain calculated by difference in grading

† Improvement in walking time and range of movement calculated as a percentage of pre-treatment measurements.

‡ Definitely significant.

The evidence is very convincing that treatment with intra-articular hydrocortisone compounds is potentially dangerous, its very success carries with it a threat of accelerating joint destruction We have reported elsewhere (Chandler et al 1958b) the production of a virtual Charcot's arthropathy in an osteoarthritic hip treated over an eighteen-month period by monthly injections of hydrocortisone This patient had obtained almost complete relief from pain when treatment was discontinued Indeed the symptomatic benefit experienced by patients may lead to a vicious circle of dependence despite worsening disease By a local mechanism in which functional improvement and relief from pain are the most important features, it seems likely that interference with the normal protective processes natural to inflammatory disease encourages a degree of weight-bearing and mobility which is inherently traumatic. Dangerous progression under these circumstances might well be expected, and has been our experience in this study Strict radiological supervision is essential if intra-articular administration of hydrocortisone and related compounds is to retain its place in the rehabilitation of the chronic rheumatic patient

Summary

18 patients with rheumatoid arthritis whose chief complaint was ascribed to involvement of the knees completed a trial of the effects of intra-articular injections of hydrocortisone acetate and hydrocortisone tertiary butyl acetate 25 knees were treated

Radiographs of the knees were obtained before and after the trial, in which physical grading and functional capacity were assessed every two weeks

Radiological deterioration was observed in 13 joints despite significant clinical improvement in the majority

Only in walking time was a significant difference apparent between patients who deteriorated radiologically and those who did not Improvement in walking time was significantly greater in the first group This group also showed a somewhat greater relief of pain after treatment, but this difference was not significant

The chief cause for radiological progression was the encouragement of a damaging level of performance by interference with a normal, locally protective mechanism.

We are indebted to Prof S J Hartfall for permission to study these patients and for helpful criticism.

REFERENCES

Chandler, G N, Wright, V, Hartfall, S J (1958a) *Lancet*, ii, 659
— Jones, D T, Wright, V, Hartfall, S J (1958b) *Brit med J* (in the press)
Empire Rheumatism Council (1955) *Ann. rheum Dis* 14 353
Kellgren, J H, Lawrence, J S (1957) *ibid* 16, 485

BARIUM MEAL AND FOLLOW-THROUGH

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Haudek (1912) observed that, if there was a considerable residue in the stomach six hours after a contrast-medium meal, this was good evidence that a disorder was present This was not a particularly challenging or arresting statement, but for some reason it struck a responsive chord A six-hour residue Here was something concrete—or very nearly concrete, bearing in mind the horrible mixtures of bread and bismuth which patients were called upon to swallow in those distant unlamented days In the succeeding forty-four years all else has changed, but not the concept To a surprising extent the medical profession is still ready to shake a wise head over a six-hour residue and set about putting it to rights Haudek may have been largely forgotten but this is his true memorial—a niche in the hall of fame as lasting as that other niche which shows with such satisfactory clarity on the lesser curves of our gastric-ulcer patients

In modern practice the six-hour residue has a significance in that it is linked with the idea of a barium meal and follow-through This is a very easy examination to ask for but not at all an easy examination to do, and it is one which is regarded with something like dismay in most X-ray departments If it is merely a matter of recording the presence or absence of a six-hour residue this is one thing, but generally the follow-through has no such clear-cut target The doctor demanding it may have made the request simply in the form of a catch-phrase, but even when this is not the case the intention is often obscure and it is left to the radiologist to do as little or as much as he thinks fit Such examinations are difficult to fit into appointment systems, and in departments where several radiologists are employed on a sessional basis the want of continuity is an additional drawback The short answer is that "barium meal and follow-through" when asked for in a routine way is likely to prove an unsatisfactory business

Radiologists have recognised this from early times, and various routines have been introduced in an effort to get over some of the difficulties One such is the double-meal technique, of which Haudek himself was an advocate but which as often as not has no other result but to make confusion worse confounded

These are perhaps somewhat controversial views, but they are held by many radiologists and for this reason it was thought worth while to see how far they could be supported and to examine critically the significance of Haudek's six-hour residue Not much has been written on these lines Shanks (1952) makes several references to Haudek's work and concludes that a six-hour residue, if of considerable size—say one-fourth to one-third of the meal—is usually of pathological import, but that even then it may be due merely to gross hypotonia and ptosis This is fair comment, but it still leaves the issue somewhat in doubt It was with this feeling that the work on which the present paper is based was undertaken

Method and Material

In the circumstances it did not seem appropriate to introduce a new routine, since the object was to check the usefulness of the ordinary everyday examination From the start, however, a special ledger was opened and all the patients in the series were put through the greater part of the procedure recommended by Shanks (1952) for full barium-meal examination The first object was to determine the percentage of cases in which there appeared to be a "significant" six-hour residue and later to follow these cases up In the course of this it was hoped to gain further insight into the true place of the follow-through in gastrointestinal investigation

In all, a thousand barium meals were studied and, making allowances for re-examination, 866 patients were included All were seen and screened before and during the taking of the meal Five basic films were exposed—two erect, an erect serial of the duodenal cap, one supine, and one prone—and if necessary other films as indicated All the patients were seen and screened again after an hour, and finally films were taken at six hours A routine dose of 'Raybar' 16 oz was given Patients were seen fasting No food or drink was allowed between the immediate examination and the one-hour stage, but, again following the technique described by Shanks, a light lunch was permitted before the six-hour film

When this plan was made it was recognised that the routine was not exhaustive It was, however, chosen as a compromise which would see the head of the meal into the proximal colon in most cases and allow a view of the often-important ileocæcal region In a large number of cases the meal was followed further in an attempt to study the whole colon, but since this was not always done the results were not included in the record

Cases referred were in three categories—(1) hospital inpatients, (2) hospital outpatients, and (3) patients referred direct by their family doctors—and thus gave a very representative cross-section

Results

A preliminary simple breakdown is interesting (see table I)

The initial examinations in the series were done between August, 1949, and April, 1951, and by a coincidence Gryspeerdt (1951) was working on a similar series at the same time but to a somewhat different end In the composition of the two sets of patients the main difference is that, whereas at Bromley the sexes were very evenly matched (439 males as against 427 females), in Gryspeerdt's series males outnumbered females in the proportion of 692 to 308 Gryspeerdt found positive evidence of abnormality in 53 9% of his cases, compared with 55 6% in my own series Taking the most common disease conditions the findings compare as shown in table II

In the present series a percentage of 9 4 diagnosed as query duodenal ulcer may seem unsatisfactory, but in the interpretation of what are after all no more than shadows there must often be room for doubt In barium-meal examinations many duodenal caps appear at some stage or other perfectly normal and can be classed as such The absolutely unequivocal recognition of a duodenal ulcer

TABLE I—PRELIMINARY BREAKDOWN

Disorder	Whole series	Male patients	Female patients
Nil	387	165	222
Gastric ulcer	59	31	28
Duodenal ulcer	210	137	73
Query duodenal ulcer	81	51	33
Carcinoma	17	9	8
Hiatus hernia	32	10	22
Others	77	36	11
Totals	866	439	427

TABLE II—COMPARATIVE FINDINGS IN TWO SERIES OF 1000 BARIUM-MEAL EXAMINATIONS

Disorder	Gryspeerdt (1951)	Present series
Gastric ulcer	17.4%	6.5%
Duodenal ulcer	25.1%	24.0%
Query duodenal ulcer	—	9.4%
Carcinoma	3.3%	1.8%
Hiatus hernia	1.1%	3.8%

is much rarer—as, for example, when an ulcer is shown barium-filled *en face* at the point of convergence of mucosal folds. By far the greater number of duodenal ulcers must be diagnosed on indirect evidence. Often this evidence is perfectly satisfactory, but there still remain the other cases (in this series 9.4%) where a conventionally normal cap cannot be shown and where at the same time a lesion cannot be sworn to. Often minor anatomical variations—for example, of the mesentery or of the gastroduodenal artery—are to blame, or the duodenal loop may be taking an independent course with confusing results.

Despite these minor differences there is quite a lot of agreement between the two series, and the results compare closely enough with those of other workers to echo a general pattern of gastrointestinal frailty.

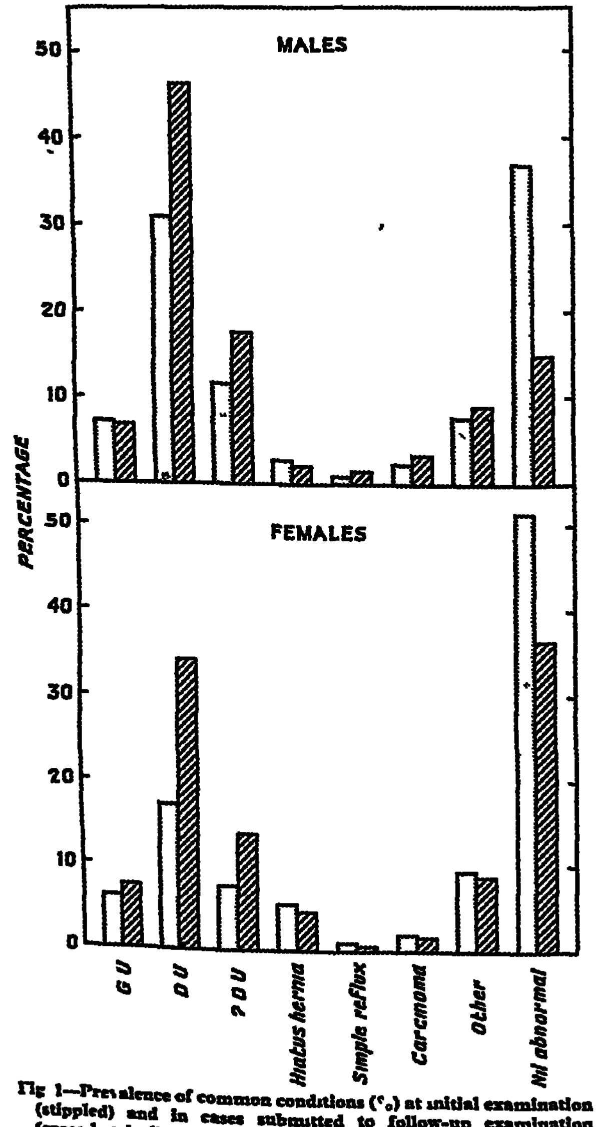

Fig 1—Prevalence of common conditions (%) at initial examination (stippled) and in cases submitted to follow-up examination (cross-hatched)

As regards the specific question of a six-hour residue two special steps were taken in each case. First, when the patient was screened at the one-hour stage the amount of barium remaining in the stomach was roughly estimated. A guess was made (in writing) as to whether or not there would be a significant residue at six hours, and finally this was checked by the six-hour film. For record purposes a quarter to a fifth of the meal remaining in the stomach at six hours was regarded as significant. Admittedly a guess made in this way is not evidence. However, for as long as medicine remains in some degree an art, impressions will be important and it was my conclusion that a practised observer could forecast a six-hour residue accurately in more than 85% of cases. Among those cases in which the residue was found it was clear that slow emptying and pathology did tend to run together in certain conditions. This is shown graphically in fig 1, in which the sexes are treated separately. The figure records the prevalence of the common conditions in the whole series and, alongside, the comparable figure in the six-hour residue cases which later constituted the follow-up.

TABLE III—RESULTS OF A FOLLOW-UP ON 215 PATIENTS WHO HAD EARLIER BEEN SHOWN TO HAVE SLOW STOMACH EMPTYING

Group	Males	Females	Totals
No dyspepsia and cases normal at repeat barium meal	26	44	70
Chronic peptic ulcer	24	28	52
Partial gastrectomy for peptic ulcer	23	9	32
Other gastrointestinal lesions proved at operation	7	8	15
Dyspepsia continuing check refused	—	3	3
Deceased	6	5	11
Failed follow-up	12	20	32
Totals	98	117	215

For both men and women the trend is similar. Duodenal ulcers and query duodenal ulcers constitute a much higher percentage of the total in the excess-residue group than in the series as a whole. Conversely the percentage of normal is much higher (especially in males) in the full series than it is in the follow-ups. Elsewhere there is little to choose. It would seem therefore that only in the duodenal-ulcer cases is there a demonstrable link, and this is, of course, what one would expect.

The Follow-up

Further to the initial analysis outlined above an attempt was made to follow up the excess-residue cases in the hope partly of checking the X-ray diagnosis and partly of assessing progress.

There were 215 follow-up cases—98 males and 117 females. The follow-up was done as a running investigation, some of the patients coming to operation within a few days of being first seen and others having had their further barium meals as late as 1957. Great difficulty was experienced in tracking down many of the patients, and when the search was abandoned in 1957 thirty-two of the original total (12 men and 20 women) had not been traced. Of the others the survivors were either re-examined by barium meal or communicated with directly or through their family doctor. A large group—15 men and 25 women—had no dyspepsia and sensibly refused another barium meal, but only 3 refusals were met with from patients still complaining. The large number who came to gastrectomy is striking. The main findings are summarised in table III.

Of the total followed up 38 2% were regarded as not having any significant upper-gastrointestinal abnormality The percentage of males in whom findings were normal was little more than half the comparable percentage in females This is probably no more than an echo of the fact, demonstrated by the initial examinations, that slow stomach emptying is more of a female than of a male characteristic The percentage of normals was smaller for both sexes in the follow-ups than in the whole series, as is shown in fig 2

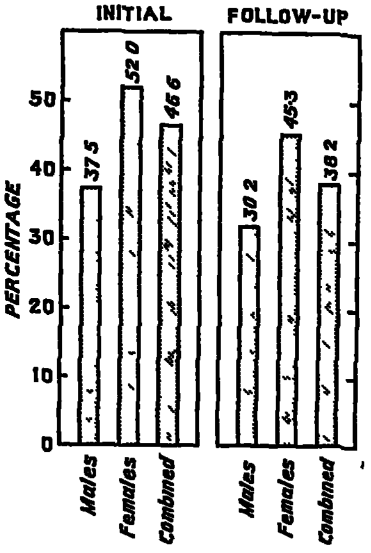

Fig 2—Prevalence of normal findings (%) at initial examination and in cases submitted to follow-up examination

Discussion

The results of this investigation may be considered first in relation to slow stomach emptying and secondly in relation to the usefulness of follow-through techniques in general

Slow Emptying

Stomach emptying certainly cannot be said to follow any simple set of rules The anatomy is straightforward enough and can be checked in any textbook, but physiology is very different The digestive work of the stomach is secretory and motor, and any study which fails to take both these factors into consideration is not likely to be conclusive This is emphasised by Hunt and Spurrell (1951), who claim that for a true estimate of gastric function a simultaneous quantitative record of secretory and motor activity during the passage of a meal is necessary They state that this can be made by their “ serial meal ” technique in which a series of standard meals is given, each being terminated by total withdrawal after different intervals of time Where the barium meal clearly fails is in providing a record only of the results of stomach motility

As well as being complex in nature, stomach emptying is difficult to control artificially, largely because of the whim of the pyloric sphincter From a practical standpoint it would help greatly in the interpretation of equivocal pyloric abnormalities if relaxation could be brought about and quick emptying assured Roka and Lajtha (1950) claim to achieve this control by means of oral procaine, but personal experiences with this method have been disappointing Methanthelinium (‘ Banthine ’) has a limited application, and Chapman et al *(1953)* have shown how barium follow-through examinations can be used to check and compare the action of drugs (including methanthelinium) on the propulsive activity of the stomach

In the final analysis Haudek may be said to be broadly supported Organic disease, especially peptic ulceration, will lead to slow emptying because of either spasm at the pylorus or stenosis There is one other well-defined group of slow emptiers these patients have the normal hyposthenic type of stomach, but with a relatively immobile high duodenal cap—a cap, in fact, in the position usually described in textbooks of anatomy If this group are kept up and about, emptying may be very slow, but their normality is shown by the ease with which emptying will occur in the recumbent position, especially prone and oblique

From the point of view of everyday practice it is important to know that delayed emptying from whatever cause can usually be recognised at the initial examination, or failing this within an hour Further radiographs to prove the obvious are unnecessary

The Follow-through

Quite a strong impression has been gained from a study of this series that little help towards a diagnosis is ever likely to come from screening or films at one hour or at six hours Furthermore when the follow-through is carried on to twenty-four or forty-eight hours it is usually equally disappointing The examination is *wasteful of time, energy, and material, and might well be* abandoned as a routine test

This judgment calls for some elaboration in view of the long-held belief that a barium meal is not complete unless it is carried through to show the large intestine The arguments for this have been well stated by Douthwaite (1956), who claims that, because a barium enema overfills the colon and irons out irregularities by hydrostatic pressure, the large bowel may be better viewed in the late stages of a meal But the introduction of the tannic-acid technique for barium enemata (Harper and Hughes 1950) has altogether changed the picture In the tannic-acid enema the stage which matters is the after-evacuation stage where there is no distension of the colon On these films in a high proportion of cases the whole length of the gut from cæcum to a point in the sigmoid can be viewed empty, contracted, and in spasm with every fold of the mucosa illustrated Nothing approaching this in usefulness is ever seen at follow-through, and if necessary air replacement can be used for additional contrast and detail The stage of filling is of little interest unless the lesion is gross—and then, of course, almost any technique will suffice With this big advance ready to hand there is no longer any need to guess at abnormalities in the colon on the follow-through appearances

It is not intended here to advocate new techniques but rather to ask for the rational use of old ones The gastrointestinal tract is too various and complex to yield up its secrets easily to any one blunderbus method A barium meal should obviously be done when abnormalities of œsophagus, stomach, or duodenum are in question For the small intestine there is likewise an appropriate technique Finally, when it comes to the colon there is only one proper complement to sigmoidoscopy, and that is a barium enema To some this may seem a long way round, but far more often than not it will prove the shortest way home

Summary

A series of a thousand unselected barium-meal examinations has been studied with a view to assessing the frequence and importance of delayed stomach emptying

In this series 98 males and 117 females were found to have a significant stomach residue after six hours, and these patients have been followed up Slow emptying is linked with duodenal abnormalities

The barium follow-through is often time-consuming and unhelpful It should not be done as a routine, and

in particular, it should never be relied on for the demonstration of the large bowel.

I have to thank the X-ray, almoner's, and outpatient departments at Bromley Hospital for assistance with the follow-up, and, in particular, Mrs C. Davies, Miss N E King, and Sister B Latchford. I received welcome assistance from Mrs L. F Steele in compiling the tables and figures

REFERENCES

Chapman, W P, Wyman, S M., Mora, L O, Gillis, M. A., Jones, C M. (1953) *Gastroenterology*, 23, 234
Douthwaite, A H (1956) *Brit med J* ii, 958
Gryspeerdt, G L (1951) *St Thom Hosp Rep* 7, 15
Handek, M (1912) *Verh dtsch Kongr inn Med* 29, 143
Harper, K., Hughes, C (1950) *J Fac Radiol., Lond* 2, 168
Hunt, J N, Spurrell, W R (1951) *J Physiol* 113, 157
Roka, G, Laytha, L G (1950) *Brit med J* i, 1174
Shanks, S C. (1952) *in* Textbook of X-ray Diagnosis (British Authors) London.

SERUM-CHOLESTEROL LEVELS AND BLOOD-PRESSURE OF ALASKAN ESKIMO MEN

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Although the Eskimo has been cited as a race which has little atherosclerosis and yet consumes a high-fat diet (Sinclair 1953), it has also been pointed out that the incidence of atherosclerosis among Eskimos is actually unknown (Keys et al. 1957), since necropsies have almost never been performed Indeed, in Alaska, most Eskimo death certificates are signed by persons other than a physician Furthermore, a large proportion of Eskimos do not have a high-fat diet (Scott 1956)

Both the serum-cholesterol level and the blood-pressure level have been associated with the incidence of atherosclerosis (Dawber et al 1957) The present study was designed to determine whether these variables are different in Eskimo men from what they are in white persons living in the United States We also wanted information about local differences in the diets of Alaskan Eskimos so that we could decide on the areas where the relationship of diet to cholesterol level might be most profitably studied

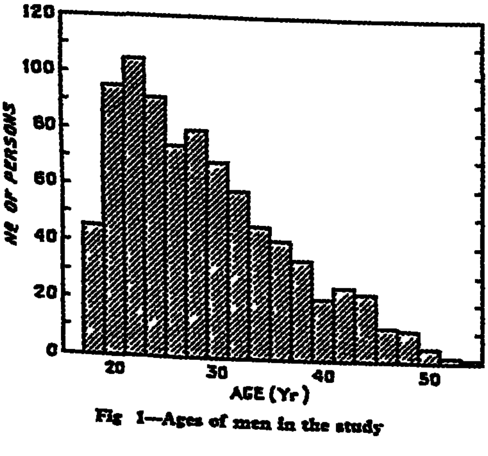

Fig 1—Ages of men in the study

CHOLESTEROL LEVELS OF ESKIMO MEN

Age	No of subjects	Mean	Cholesterol level	
			Standard deviation	Range
17–19	90	187 8	39 1	109–386
20–24	247	201·9	3[illegible] 9	123–302
25–29	162	219·7	47 1	122–373
30–34	144	219·7	39 1	133–329
35–39	91	233 3	40·1	166–405
40–44	58	234 5	45 5	131–354
45–49	26	243·4	51·4	179–378
50–53	4	200·5		186–217

Methods

The subjects were 842 Eskimo men between the ages of 17 and 53 who were members of the Alaska National Guard No physical examination is required for membership of the Guard, although persons with gross physical abnormalities or active tuberculosis are usually excluded It was estimated that 80% of the subjects were full Eskimos Included also were one small group of 28 Aleuts and another of 19 Athabascan Indians Cholesterol was determined on non-fasting serum by the method of Abell et al (1952) Twenty-two of the serum samples were sent to the laboratory of the Heart Disease Epidemiology Study, Framingham, Massachusetts, where independent determinations gave results 4 6±1 2 mg per 100 ml higher than our results Blood-pressure was determined in the sitting position

Results

The mean cholesterol level of all persons tested was 214 4 mg per 100 ml with a standard deviation of 40 9 (see table) There was considerable variation of mean cholesterol level depending on geographic location (fig 2) The highest mean level was 293 mg (S.D 64) in 11 subjects, while the lowest mean level was 171 (S D 32) in 15 subjects Men from four of the forty-three villages studied had mean cholesterol levels significantly higher than the average of all Eskimos, while representatives of ten other villages had significantly lower levels, using a 20-to-1

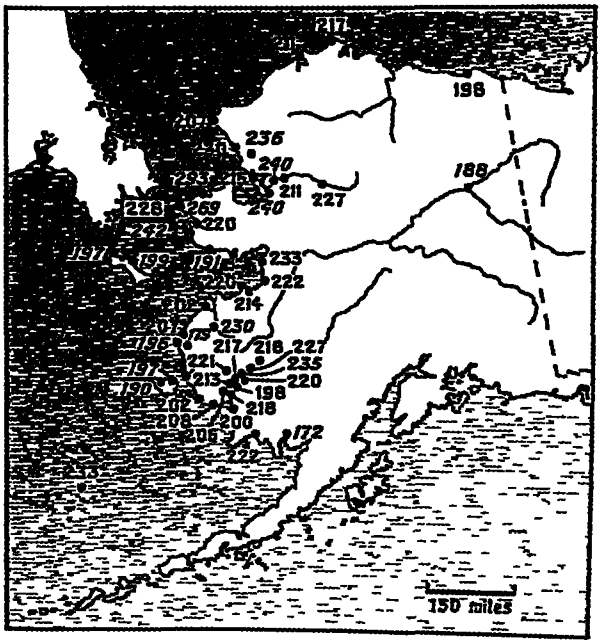

Fig 2—Mean cholesterol levels of men in the study Figures in italics are significantly higher or lower than the mean of all subjects.

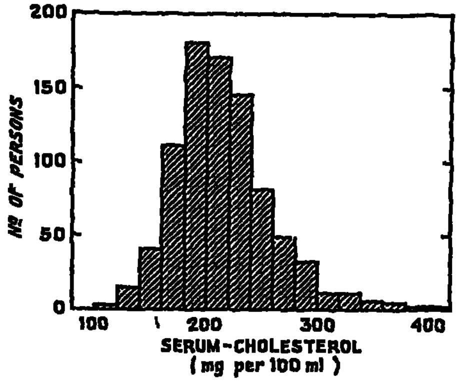

Fig 3—Cholesterol levels of Eskimo men Median level is 202 mg per 100 ml

criterion of significance The numbers in italics in fig 2 represent these villages However, the only generalisation possible from this figure is that northern Eskimos have higher cholesterol levels than southern Eskimos (*217 8±2 0 mg* per 100 ml as opposed to 210 2±1 9 mg)

There was some dependence of cholesterol level on age (r=0 377) The least squares equation of this dependence was

Cholesterol level=158 8+1 97×age

The results shown in the table resemble closely those obtained in normal men in the United States (Lewis et al 1957) In calculating probability of significance of differences of cholesterol levels, a correction was made for age dependence

Different blood-pressure readings were obtained by different people, and also by the same person on different days Our correction for these possible errors may have minimised actual differences between villages The average systolic pressure found was 126 9, the average diastolic pressure was 74 3, and the average pulse pressure was 52 6 mm Hg In further calculations, the mean of the systolic and diastolic pressures was used The average mean blood-pressure of all men tested was 100 6 (S D 10 1)

Of the 842 men tested, 22 had mean blood-pressures above 125 mm Hg They came from 16 villages, but no village had more or less persons with high blood-pressure than would be expected from random sampling Of the forty-three villages from which 10 or more men were tested, four were found in which the men had average mean blood-pressures significantly higher than the average for all villages In another four, the values were significantly low The values obtained and probability of significance for each of these eight villages were 111 6, 0 003, 106 2, 0 004, 105 0, 0 022, 104 4, 0 008, 96 2, 0 010, 95 9, 0 006, 94 6, 0 017, 91 7, <0 0001 That these differences were real seemed evident, since mean blood-pressures of men from two villages measured by the same persons on the same day were 104 4±1 4 and 94 5±2 5 These two villages, though only 14 miles apart, have a quite different ethnic background, and the populations do not intermingle

There was a low correlation of mean blood-pressure with age (r=0 142) At age 20, mean blood-pressure was 98, while at age 45 it was 104 There was little or no correlation between mean blood-pressure and serum-cholesterol (r=0 066)

Discussion

In the first study of cholesterol levels in Eskimos, Corcoran and Rabinowitz (1937) found these levels to be very low The mean of 27 determinations was 141 mg per 100 ml Subsequent investigations on other small groups of Eskimos (Wilber and Levine 1949, Sinclair et al 1949, Rodahl 1954a, Pett and Lupien 1958) have failed to confirm these low levels, and are in agreement with our results Although Alaskan Eskimos as a group appear to have normal serum-cholesterol levels, the geographic variation in level deserves further study

The measurements of blood-pressure in this study are in essential agreement with, although slightly higher than, those found in a large series of men in the United States (Robinson and Brucer 1939). In any case we, unlike Rodahl (1954b), have found no evidence of unusually low blood-pressures in Eskimos

Summary and Conclusions

The mean serum-cholesterol level of 842 Eskimo men did not appear to be unusual, but there were significant differences in men from different localities in Alaska Measurements of blood-pressure showed much less variation, although here again geographic differences were found

REFERENCES

Abell, L L , Levy, B B , Brodie, B B , Kendall, F E (1952) *J biol Chem* 195, 357

Corcoran, A C , Rabinowitz, I M (1937) *Biochem J* 31, 343

Dawber, T R , Moore, F E , Mann, G V (1957) *Amer J publ Hlth*, 47 (suppl to no 4), 5

Keys, A , Anderson, J T , Grande, F (1957) *Lancet*, i, 66

Lewis, L A , Olmsted, F , Page, I H , Lawry, E Y , Mann, G V , Stare F J , Hanig, M , Lauffer, M A , Gordon, T , Moore, F E (1957) *Circulation*, 16, 227

Pett, L B , Lupien, P J (1958) *Fed Proc* 17, 488

Robinson, S C , Brucer, M (1939) *Arch intern Med* 64, 409

Rodahl, K (1954a) *Trans Amer Coll Cardiol* 4, 193

— (1954b) *ibid* p 273

Scott, E M (1956) *Nutr Rev* 14, 1

Sinclair, H M (1953) Proc Nutr Soc 12, 69

Sinclair, R G , Brown, G M , Cronk, L B (1949) *Fed Proc* 8, 1949

Wilber, C G , Levine, V E (1949) *Exp Med Surg* 8, 422

TYPING OF Q-PHASE INFLUENZA-A VIRUS BY SERUM-NEUTRALISATION TESTS IN MONKEY-KIDNEY CULTURES

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THE method currently used for typing strains of influenza virus is based on hæmagglutination inhibition by type-specific sera This method is simple and rapid and gives reliable information in the majority of cases It is not, however, satisfactory for certain strains (Q) which have been described by van der Veen and Mulder (1950) These Q strains combine very poorly with the homologous antibody responsible for inhibiting hæmagglutination and give low titres in hæmagglutination-inhibition tests compared with strains in the reactive or P phase When injected into ferrets Q-phase strains do, however, stimulate the production of antibodies which react with strains in the P phase, and Q-phase strains are usually typed indirectly by the preparation of an antiserum which is subsequently tested by hæmagglutination inhibition with a strain in the P phase This method is, however, laborious and wasteful of laboratory animals

Vogel and Shelekov (1957) described an adsorption-hæmagglutination technique for detecting influenza virus grown in monkey-kidney cultures By this technique influenza virus is grown in monkey-kidney tissue cultures to which guineapig red blood-cells are subsequently added The red cells are adsorbed to the infected tissue cells in a characteristic pattern This has been called hæmadsorption By this technique we have obtained

TABLE I—SERUM-NEUTRALISATION TESTS IN MONKEY-KIDNEY TISSUE CULTURE WITH STOCK INFLUENZA-A VIRUS STRAINS AND ANTISERA

Virus strain	Serum					
	Shope	PR8	WS	FM-1	A/Ned/36/56	A/Singapore/1/57
Shope	320	<20	<20	<20	<20	<20
PR8	<20	640	80	<20	<20	<20
WS	<20	20	160	<20	<20	<20
FM-1	<20	<20	<20	1280	<20	<20
A/Ned/36/56	<20	<20	<20	40	80	<20
A/Singapore/1/57	<20	<20	<20	<20	<20	2560

The figures denote the reciprocals of dilutions of sera inhibiting 100 hæmadsorption doses of virus

type-specific serum-neutralisation reactions with strains of influenza virus in both the P and the Q phase

Materials and Methods

Virus strains —Standard strains—Shope, PR8, WS, FM-1, and A/Ned/36/56—were received from the World Influenza Centre Strains isolated in the recent epidemic of Asian influenza were received from various laboratories of the Public Health Laboratory Service, all these strains were isolated in fertile eggs and were received as early passage fluids

Sera —Standard sera for the different type strains employed were supplied by the World Influenza Centre Antisera against some of the Asian-influenza strains were prepared by intranasal inoculation of ferrets with freshly isolated strains

Monkey-kidney cultures —Trypsinised cell suspensions were grown for 5 days in stationary tubes with a medium consisting of 0 5% lactalbumin hydrolysate and 0 5% ox serum in Hanks' solution with 100 units penicillin and 100 µg streptomycin per ml This medium was then replaced by Eagle's medium (1955) without serum, the cultures were inoculated and incubated in a roller drum

Virus titrations —Tenfold dilutions of the virus under test were inoculated in volumes of 0 1 ml into a pair of monkey-kidney cultures After 48 hours' incubation 0 2 ml of a 0 4% suspension of freshly washed guineapig red cells was added The tubes were kept at room temperature for 10 minutes and then examined under the microscope for hæmadsorption The end-point was taken as the highest virus dilution showing hæmadsorption

Serum-neutralisation tests —Serial dilutions of standard sera in 0 5 ml volumes were mixed with equal volumes of a virus dilution containing 100 hæmadsorption doses, incubated for half an hour at 37°C and inoculated into tubes of monkey-kidney tissue These tubes were then sloped in a rack so that the serum-virus mixture was in contact with the tissue cells After half an hour at room temperature the fluid was removed from the tubes and replaced by fresh medium, and the tubes were incubated in a roller drum for 48 hours at 37°C, 0 2 ml of a 0 4% suspension of guineapig red cells was then added to the tubes, which were examined for hæmadsorption. The neutralisation titre was taken as the highest final serum dilution showing complete inhibition of hæmadsorption

Hæmagglutination-inhibition (H I) *tests* —These were performed in 'Perspex' plates using 0 25 ml volumes of serial dilutions of sera treated with cholera-filtrate to remove any non-specific inhibitors of hæmagglutination, 0 25 ml of a virus dilution containing 8 agglutinating doses, and 0 25 ml of a 0 5% suspension of washed fowl cells The serum dilution showing 50% agglutination was taken as the end-point (World Health Organisation 1953)

TABLE II—COMPARISON OF H I TESTS AND SERUM-NEUTRALISATION TESTS WITH STRAINS OF INFLUENZA-A VIRUS IN THE P AND Q PHASES

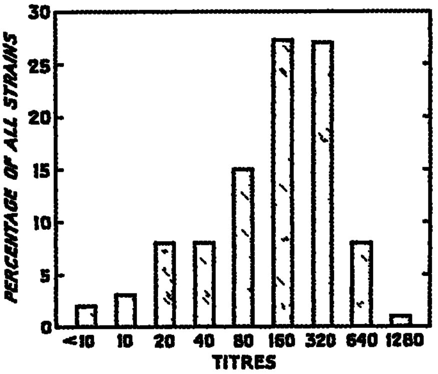
Virus strain	H I tests		Serum neutralisation tests	
	Serum Q-phase A/England 530 57	Serum P-phase A England 550 57	Serum Q-phase A England 530 57	Serum P-phase A England 550 57
Q-phase A England 530 57	<10	<10	640	640
P phase A England 550 57	320	320	640	640

The figures are the reciprocals of the dilutions of sera

Results

The results of serum-neutralisation tests with standard strains of influenza-A virus are shown in table I Cross-reactions were rarely observed, and except for that between PR8 and WS they were of small degree As in the H I tests crossing was not observed between Asian strains and any of the earlier influenza-A viruses

Table II shows the results of H I tests and serum-neutralisation tests with strains of influenza-A virus in the P and Q phase It will be seen that in the H I tests the Q-phase strains did not combine with antibody in sera prepared in ferrets against either P or Q phase viruses, whereas both P and Q strains combined equally well in the serum-neutralisation tests It is clear from these results that strains in the Q phase may be easily identified by serum-neutralisation without recourse to making a homologous serum The frequency with which Q-phase strains were encountered in 1957–58 is shown in the accompanying figure All the tests included in this figure were done with one of the three Asian-influenza ferret antisera with titres varying between 1/160 and 1/320 when tested against A/Singapore/1/57 21% of 500 strains examined gave titres of 1/40 or less 10 of these have been tested and successfully typed by the hæmadsorption technique described above



Frequency distribution of titres of 500 strains of Asian-type influenza-A virus in H I. tests with A/Singapore/1/57 ferret sera

Preliminary results of work in progress with human convalescent sera suggest that rises in antibody against Asian influenza are detected more frequently by the hæmadsorption technique than by H I tests

Summary

Asian strains of influenza-A virus in the Q or non-reactive phase, determined by the standard hæmagglutination-inhibition test, can be typed fairly simply by a serum neutralisation test in monkey-kidney tissue culture using the hæmadsorption technique of Vogel and Shelekov (1957)

I should like to thank Dr F O MacCallum for encouragement in this work, and Dr A Isaacs (World Influenza Centre) for supplying some strains and sera

REFERENCES

Eagle H (1955) *Science*, 122, 501
van der Veen, J , Mulder, J (1950) Studies on the Antigenic Composition of Human Influenza Virus A Strains Leiden
Vogel, J , Shelekov, A (1957) *Science*, 126, 358
World Health Organisation (1953) *Tech Rep Wld Hlth Org* no 64

HYPERPYREXIA IN ENCEPHALITIS TREATED BY HYPOTHERMIA

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Sporadic cases of encephalitis have an uncertain prognosis, the outcome depending partly on the success of prophylaxis and treatment of the complications of the coma One feature of the disease which may cause death is hyperpyrexia A case is here described of encephalitis complicated by rapidly increasing pyrexia in which the temperature was reduced by hypothermia induced by drugs and physical cooling and maintained at a subnormal level until consciousness returned

Case-report

A lift attendant, aged 30, was admitted on Feb 12, 1958 Eight days before admission he had had a febrile illness with sore throat and cough, diagnosed as " influenza " All members of the family had a similar illness at the time After four days he had recovered sufficiently to resume work Two days later he complained of pains in the back and was sent home from work at midday Arriving home he slept from 2 P M to 8 30 P M on a couch, refused food, did not reply to his wife's questions, and then retired to bed He made no complaint of headache That night he was extremely restless in bed, sweated profusely, and shouted several times Next morning his wife was unable to rouse him and noted that his whole body was shaking On her return to the bedroom after summoning the doctor she found him sitting on the floor in a pool of urine, he did not recognise her, nor did he answer her questions He was admitted in a stuporose state

His past history included partial gastrectomy for a duodenal ulcer in 1953 and deterioration of visual acuity in 1954, owing to familial macular degeneration At that time a full neurological examination had been performed by Dr E A Blake Pritchard and ophthalmological examination by Mr C Dee Shapland, these provided very useful records for purposes of comparison Since then he had been able to read only with the aid of a powerful hand lens in addition to glasses

On admission his temperature was 100 4°F, pulse-rate 100 per min , pulse regular, respiratory rate 28 per min He was very agitated and restless, did not reply to questioning but responded to painful stimuli, and greatly resented physical examination He had neck rigidity, trismus, and photophobia His pupils were equal and circular, and reacted to light His fundi showed bilateral macular degeneration, with optic atrophy on the right side, the disc margins were sharp No abnormality was detected in the remaining cranial nerves In his limbs the tone varied from time to time with spontaneous movements, he had continuous muscle twitchings His tendon reflexes were weak and plantar responses flexor His respiratory excursion was noticeably shallow and he was cyanosed

Investigations —White blood-cells 9800 per c mm (polymorphs 70%, lymphocytes 26%, monocytes 4%) Urine normal Chest X-ray normal Lumbar puncture yielded cerebrospinal fluid (C S F) under pressure of 300 mm H_2O (but patient was struggling) containing protein 110 mg per 100 ml (globulin, slight excess (Pandy test)), white blood-cells 31 per c mm (lymphocytes 30, polymorphs 1), red blood-cells 1 per c mm , chloride 700 mg per 100 ml , sugar 95 mg per 100 ml No bacteria were seen on Gram and Ziehl-Nielsen staining

Diagnosis and treatment —The diagnosis was considered to be either acute encephalitis, possibly influenzal, or fulminating tuberculous meningitis The patient was seen by Dr W W Gooddy, who agreed and advised a further lumbar puncture the following day to see whether by then the C S F sugar and chloride levels had changed Repeat lumbar puncture on the following morning yielded C S F under a pressure of 300+ mm H_2O, containing protein 180 mg per 100, white blood-cells 66 per c mm (polymorphs 57%, lymphocytes 38%, monocytes 5%), red blood-cells 9 per c mm , chloride 725 mg per 100 ml , sugar 58 mg per 100 ml

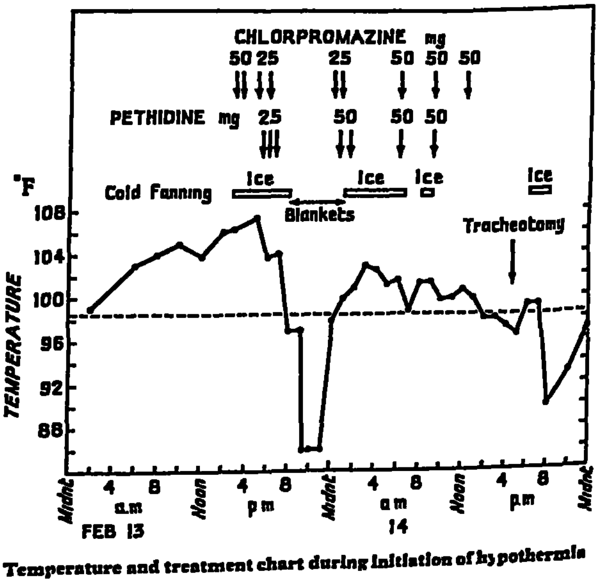
Acute encephalitis was diagnosed and treatment was directed to preventing complications until consciousness returned—particularly of the chest in view of the persistent cyanosis and shallow breathing An endotracheal tube was inserted to maintain a good airway A tracheotomy was performed the following afternoon by Mr B V McEvedy

At 2 A M that morning the patient's temperature was 99°F, at 6 A M 103°F, at 8 A M 104°F, at 10 A M 105°F, cold sponging and fanning were instituted At noon the temperature was still 105°F, by 2 P M it had risen to 106 2°F, and by 2 30 P M it was 106 4°F All temperatures were taken rectally

Induction of hypothermia —Since the continued rise of temperature seemed likely to prove fatal the decision was made to use hypothermia in an attempt to reduce the temperature to normal Chlorpromazine alone was given initially (since pethidine was contraindicated by the shallow breathing and cyanosis) and the trunk and limbs were covered with ice. Shivering was not entirely prevented by chlorpromazine, and in the first two hours the temperature did not fall, in fact it rose to 107 6°F at 5 30 P M During this period the patient's respiratory excursions improved greatly and his cyanosis lessened Pethidine was then administered intravenously, in conjunction with chlorpromazine this controlled the shivering and the temperature fell to 97°F by 8 P M The ice, ice water, and fans were removed and blankets placed on the patient Despite this his temperature continued to fall, and an hour later it had reached 86°F He was then warmed, but his temperature rose to 103°F With further cooling it fell to 90°F and then rose to 97°F It was then maintained at 96–98°F until consciousness was regained sixty-five hours after admission The amounts of drugs given and temperature chart are shown in the accompanying figure

Further treatment and progress —During the period of unconsciousness the water and electrolyte balance was maintained principally by means of 2 5% glucose in 0 45% saline solution administered initially through an intravenous needle, but later through a polyethylene catheter inserted in the femoral vein His urine volume was well maintained after an initial period of oliguria No cardiac arrhythmias were detected

After regaining consciousness the patient was very restless, requiring sedatives during the next four days to control his agitation His behaviour then returned to normal The tracheotomy tube was removed on Feb 20



Temperature and treatment chart during initiation of hypothermia

Physical examination a week after return of consciousness showed nystagmus to the left. Otherwise there was no abnormality which had not been noted four years previously He had a retrograde amnesia dating back to about six weeks before the onset of coma, this defect of memory still persisted two months later He is also forgetful of recent events and complains of lack of ability to concentrate

Electroencephalography a fortnight after admission showed generalised abnormalities with rhythms down to 4 C.P S in the frontal areas A further examination a month later showed the expected improvement with a stable dominant α rhythm

Complement-fixation tests performed by the Central Public Health Laboratory, Colindale, on blood specimens, taken on the second day of his illness and three weeks later, were negative for antibodies to influenza A and B, the adenoidal-pharyngeal-conjunctival (A P C) group of viruses, Q fever, psittacosis, and streptococcus M G

The patient was discharged on March 17

Discussion

This illness was probably sporadic encephalitis in a patient who had had an influenzal-like illness two days previously and not "influenzal encephalitis", since antibodies to the viruses of influenza A and B could not be detected in the serum during the acute phase

The principal purpose in inducing hypothermia was to avert a known fatal complication of encephalitis—namely, hyperpyrexia due to disturbance of the heat-regulating centre A second purpose was to reduce oxygen consumption in a patient with persistent cyanosis Both these aims were achieved The possibility of using hypothermia in the treatment of hyperpyrexia was mentioned by Gray (1957) No reference to its use in the hyperpyrexia of encephalitis has been found Rowbotham et al. (1957), however, employed hypothermia to reduce cerebral metabolism and prevent death from hyperpyrexia in a case of head injury with a rising temperature, it is also used in neurosurgical procedures

Shivering was not abolished in this case by chlorpromazine alone, possibly the dosage was insufficient No cooling occurred while the patient was shivering Respiratory rate and depth were, however, greatly improved either by the chlorpromazine or by the stimulus of ice on the skin The addition of pethidine controlled the shivering, and the rectal temperature then fell very rapidly to 86°F (30°C) as the result of skin cooling by ice water During rewarming the rectal temperature rose to 102°F—not the 96–98°F aimed at The difficulty of controlling the cooling and warming of this patient emphasises the disadvantages of the technique of achieving hypothermia by skin cooling This difficulty was pointed out by Khalil and Mac Keith (1954), who advocated the use of an intragastric balloon irrigated with ice water—a method which proved satisfactory in rabbits and in a boy of 16 Khalil (1958) has reported the successful use of this method in the removal of intracranial tumours in two cases

The reduction of cerebral metabolism is greatest with reduction in temperature to 82°F, below that temperature further cooling results in little decrease of metabolic rate Stone et al (1956) showed that shivering causes a pronounced increase in cerebral metabolism, underlining the importance of abolishing shivering in these cases

In the present case the cause of the shallow breathing on admission was not clear An endotracheal tube was inserted initially so that respiration could be assisted if necessary Some difficulty was experienced in removing secretions, and the trecheotomy might have been performed earlier with advantage Efficient physiotherapy throughout the period of coma and the following days, together with penicillin, averted aspiration pneumonia

We thank Dr W Brooks and Dr P J Verrill for advice with regard to hypothermia, and Sister B Sowden and the nursing staff of ward 4

REFERENCES

Gray, J C (1957) *Lancet*, i, 383
Khalil, H H (1958) *ibid* i, 1092.
— Mac Keith, R C (1954) *Brit med J* ii, 734
Rowbotham, G F, Bell, K, Akenhead, J, Cairns, A (1957) *Lancet*, i, 1016,
Stone, H H, Donelly, C, Frobese, A S (1956) *Surg Gynec Obstet* 103 313

CHEST PHYSIOTHERAPY
DURING INTERMITTENT POSITIVE-PRESSURE RESPIRATION

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THE introduction of intermittent positive-pressure respiration (I P P R) by Lassen (1953) was an important advance in the treatment of respiratory paralysis This method was first used in treating cases of poliomyelitis, but its scope has since been extended to include treatment of cases of acute polyneuritis, tetanus, barbiturate poisoning, myasthenia gravis, bronchitis with emphysema, and other conditions When artificial respiration is required for patients with paralysis of the respiratory muscles, the patient is normally too weak to cough sufficiently to clear the bronchial tree of secretions so that there is a special liability to pulmonary complications

In the prophylaxis and treatment of these complications, which may well determine the final outcome, physiotherapy to the chest is of prime importance (Lassen 1953, Smith et al 1954) It is normally given in the form of "vibration" to the chest wall followed by powerful compression of the chest, the whole manœuvre occupying less than one second and being repeated with each breath The patient is postured to drain the part of the lung receiving treatment We consider here the mechanisms by which this physiotherapy is effective

Modern electronic manometers have played an important part in the elucidation of mechanical properties of the chest, and important contributions have thus been made in recent years to knowledge of both normal and abnormal lungs and thoracic cage In the present investigation manometers of this type have been used to measure the pressure changes in the thorax during artificial respiration with and without chest physiotherapy, and this has thrown light on the mechanism by which chest physiotherapy produces its effect

Methods

Œsophageal pressure was measured by an air-filled polyethylene tube 1 5 mm bore, enclosed over the terminal 18 cm by a latex balloon which tolerated the introduction of 2 ml air when lax and free before any pressure change The part of the tube inside the balloon had a hole in its wall every 2 cm All pressure changes were measured with a capacitance manometer and recorded on a direct writing recorder Air flow was measured by a modified Lilly (1950) pneumotachograph

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* Work done while holding a Rhodes scholarship

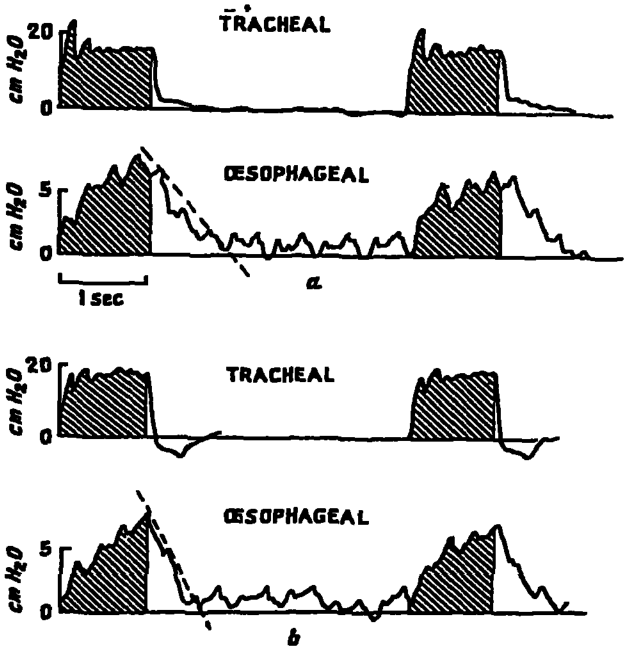

Fig 1—Pressure in trachea and œsophagus during I P P R Inspiratory period is hatched In fig 1b expiration is expedited by short negative-pressure phase, as is shown by slope of dotted line

In order to determine the air flow in centimetres per second the coronal diameter of the trachea was measured on a radiograph taken in the expiratory position The diameter of the tracheotomy tube was known, and its apparent diameter was measured on the radiograph This enabled a correction to be made to the radiographic diameter of the trachea to provide the real diameter The sagittal diameter was taken to be five-sixths of the coronal diameter (Engel 1947), and the cross-sectional area of the trachea was derived from these figures Six patients were receiving I P P R from a 'Radcliffe positive-negative-pressure respiration pump' (Russell et al 1956), two were on pumps of comparable design but with no negative-pressure phase Every patient had a cuffed rubber tracheotomy tube (Spalding and Smith 1956) The cuff was inflated sufficiently to provide an airtight fit in the trachea Subatmospheric pressure is referred to as negative pressure

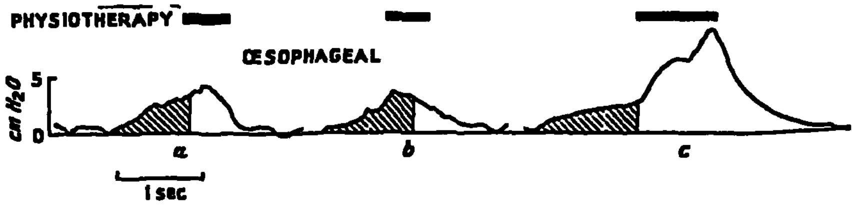

Fig 3—Effect of less usual types of physiotherapy on œsophageal pressure (a) with hands on anterior and posterior aspects of chest, (b) with pressure to abdomen only, (c) with synchronous pressure to abdomen and chest

Results

During inspiration by I P P R the pressure in the trachea is raised and air enters the lungs As this occurs and the lungs inflate, the pressure in the œsophagus rises (fig 1a) During expiration the tracheal and œsophageal pressures fall rather steeply provided a satisfactorily free passage is available for the expired air Expiration may, however, be expedited by a negative pressure in the trachea (fig 1b), and, as this is the pressure pattern we normally use clinically, it has been used during this investigation The œsophageal pressure is modified during physiotherapy, and fig 2 shows œsophageal pressures with physiotherapy occurring during inspiration (fig 2a), early in expiration (fig 2b), and in the middle of the expiratory period (fig 2c) Fig 2b and c were taken during unusually vigorous physiotherapy, and in normal treatment the œsophageal pressure is raised to a peak of only about 4 cm water The timing of the compression varied from one physiotherapist to another All started at the beginning of expiration The majority gave a preliminary period of "vibration", followed by forceful compression in the middle of the expiratory period *(fig 2c), when they could feel that the chest had* virtually returned to the resting position Others omitted the vibration and compressed during the period of rapid initial deflation in early expiration (fig 2b)

Physiotherapy is usually given with the hands placed close together over the part of the lungs to be treated Fig 3a shows the effect of holding the hands on the posterior and anterior aspects of the chest, another method commonly used Fig 3b shows the effect of pressure on the abdomen only, and Fig 3c of synchronous pressure on the chest and abdomen This last produces a very pronounced rise in œsophageal pressure, but as it requires two operators it is inconvenient in practice Fig 4 shows the effect on the œsophageal pressure of chest compression of the normal duration 0 5 sec, and of a longer period—1 25 sec

The rate of air-flow in and out of the lungs is related to the œsophagotracheal pressure, since the œsophageal pressure is closely related to the intra-pleural pressure (Dornhorst and Leathart 1952, Fry et al 1952) Therefore the rise in œsophageal pressure during physiotherapy (fig 2b) accelerates expiration A greater and more prolonged alteration in this pressure gradient can, however, be produced by increasing the negative pressure to the trachea during expiration Fig 5 shows the maximal negative pressure produced in

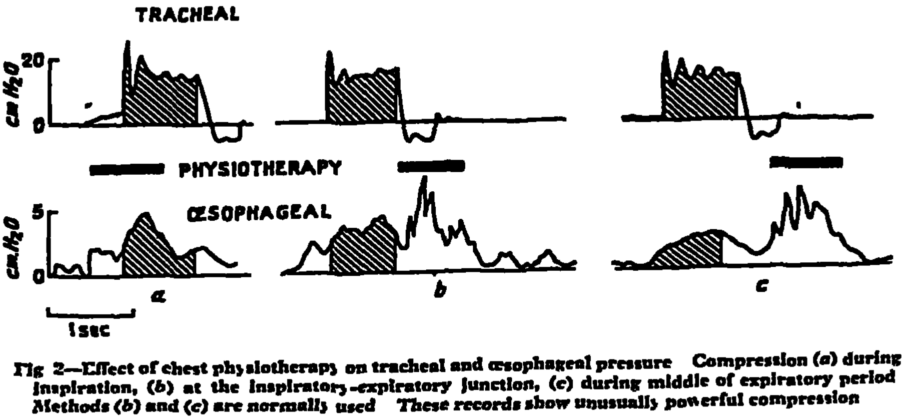

Fig 2—Effect of chest physiotherapy on tracheal and œsophageal pressure Compression (a) during inspiration, (b) at the inspiratory-expiratory junction, (c) during middle of expiratory period Methods (b) and (c) are normally used These records show unusually powerful compression

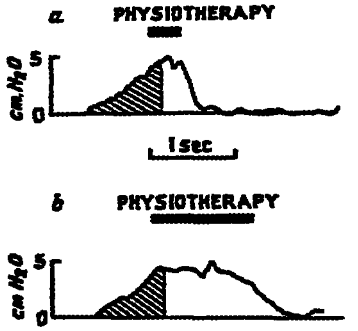

Fig 4—Effect of duration of physiotherapy on œsophageal pressure (a) brief compression (less than 0·5 sec.), (b) prolonged compression (1·25 sec.)

the trachea and œsophagus by the Radcliffe positive-negative-pressure respiration pump One of the features of this respiration pump is that negative pressure is produced by gravity and therefore comes into operation without delay It produces a negative pressure in the trachea of about 10 cm water so that the œsophagotracheal pressure gradient is greater than that produced by physiotherapy Moreover, the œsophageal pressure is still raised when this negative pressure is applied to the trachea, so that the pressure gradient is further increased (fig 5) As physiotherapy usually causes a pressure difference of about 4 cm. water, the negative pressure produced by the pump results in a much greater œsophagotracheal pressure difference.

These findings were supported by studies of the air-flow through the tracheotomy tube. The expiratory flow was expedited by negative pressure in the trachea, which increases the flow considerably more than does chest compression given at the inspiratory-expiratory junction. Application of compression later in the expiratory period (fig 2c) caused very slight alteration in air-flow Maximum air-flow recorded with the positive-negative-pressure respiration pump was less than 2 litres per sec, corresponding to a speed of 16 m per sec (51 ft. per sec., 36 miles per hour) compared with speeds close to that of sound in the trachea during normal coughing (Ross et al 1955)

Discussion

Physiotherapy to the chest is an effective method of removing secretions from the lungs There are two principal mechanisms by which it may act

1 By raising the intrathoracic pressure as a whole it causes air to be rapidly expelled from the lungs, and possibly the blast of air thus created carries secretions along, as in the normal cough sputum is carried from the trachea to the exterior

2 By local compression of the consolidated lung the retained material may be squeezed out along the bronchus, as tooth-paste is squeezed out of its tube This has been observed during bronchoscopy (A. C. Smith, personal communication)

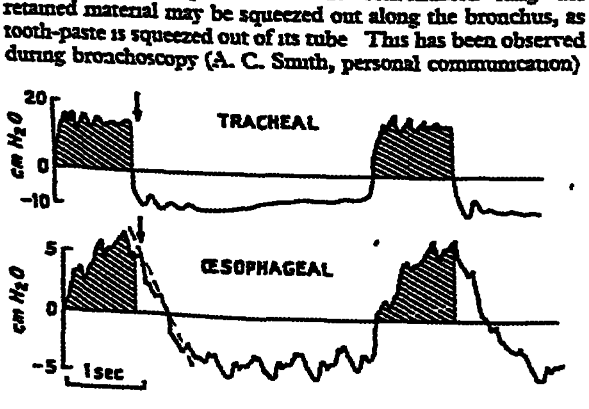

Fig 5—Tracheal and œsophageal pressures with negative pressure of 7-10 cm. water in trachea throughout expiration. At arrow œsophagotracheal pressure gradient is about 13 cm. water

For a given part of the respiratory cycle the air-flow is related to the pressure difference between the œsophagus and trachea, and the records (figs 2 and 5) show that a greater pressure difference and greater air-flow can be produced by the respiration pump than by the physiotherapist Clinical experience indicates, however, that a negative-pressure phase from a respiration pump is a totally inadequate substitute for chest physiotherapy The increased expiratory flow with physiotherapy is not even capable of expelling loose secretions through the tracheostome, and endotracheal suction through a soft rubber catheter is necessary to remove secretions when they have reached the larger bronchi Moreover, physiotherapy during the middle of the expiratory period (fig 2c) is as effective as in early expiration (fig 2b), although the air-flow is very much less It therefore seems probable that the vital part in physiotherapy of the chest is the direct squeezing of that part of the lung beneath the physiotherapist's hands and that this pushes the secretions out into the main bronchi Machines have been designed which are intended to clear secretions from the chest of a paralysed patient, their principle being to inflate the lungs to a considerable pressure and suddenly apply negative pressure to the trachea This produces a considerable outflow of air in a short time, though probably the flow rate is much slower than in normal coughing (Whittenberger 1957), but it does not simulate the squeezing of a consolidated lobe that appears to be so valuable in chest physiotherapy This may account in part for the fact that these "cough-machines" have not been more widely adopted

During normal respiration the intrathoracic pressure is subatmospheric during inspiration, and this assists the return of venous blood to the heart During artificial respiration by I.P.P.R. (and similar considerations apply to the tank respirator) the pressure in the chest is raised during inspiration, impeding return of blood to the heart (Werkö 1947), and the maintenance of cardiac output may depend on compensatory mechanisms Physiotherapy to the chest further increases the intrathoracic pressure In our experience, however, this hardly ever justifies the omission of chest physiotherapy even in a patient who is very ill and whose compensatory mechanisms are suspect. In such a patient we sometimes give physiotherapy in the horizontal and head-down positions, but omit the head-up position normally used for treating the upper lobes Clinical experience has shown that each period of chest compression need only be brief, up to about 0·75 sec. (fig 2b and c, fig 4a), for prolonged compression appears to be no more effective For the same peak œsophageal pressure, periods of compression of 0·4 sec. and 1·25 sec. (fig 4) result in an increase in mean œsophageal pressure of 50% and 200% respectively The shorter period therefore places a smaller strain on the circulation.

Summary

Physiotherapy to the chest is an effective method of removing secretions from the lungs of patients with respiratory paralysis

The life-saving benefits of physiotherapy are due to direct squeezing of the part of the lung beneath the physiotherapist's hands, not to a general increase in the rate of expiratory flow

We wish to thank Dr W Ritchie Russell and Dr A Crampton Smith for their advice and assistance

References overleaf

FAMILIAL OUTBREAK OF ACUTE GLOMERULONEPHRITIS DUE TO GRIFFITH TYPE-1 STREPTOCOCCUS

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SHEFFIELD ROYAL INFIRMARY

THE opportunity of investigating, at an early stage, the bacteriology of familial outbreaks of acute glomerulonephritis does not often arise

We have been unable to trace any report of a family or community outbreak in which infection with the β-hæmolytic streptococcus, Lancefield group A, Griffith type 1, resulted in acute nephritis in as many as four members out of ten affected

In the familial outbreak of acute nephritis we describe, such a "nephritogenic" action has been demonstrated for a type-1 streptococcus

History of Outbreak

The family Q consists of father, aged 40, mother aged 38, and nine children aged 17–1½ years The family lives in a semidetached house with 6 rooms (3 bedrooms) in a large village on the outskirts of Sheffield None of the family had suffered from scarlet fever, rheumatic fever, or frequent attacks of acute tonsillitis and none had undergone tonsillectomy

The main clinical and bacteriological features are summarised in the accompanying table In the first week of February, 1958, Joan Q contracted severe acute tonsillitis Three to four weeks later her sisters Jane and Mary developed severe attacks of the same illness The following week John, Martha, Francis, and Rose Q developed mild infections of the upper respiratory tract within a few days of each other Kenneth Q, the youngest, fell ill with cervical adenitis and acute otitis media after the four preceding children had recovered Both parents developed sore throats a week after Kenneth had fallen ill, and the mother subsequently had monoarthritis The only member of the family not to suffer some clinical illness up to this point was the eldest son, Harold Only Kenneth received systemic penicillin Some of the others were treated with oral penicillin

Case 1 —Joan Q was admitted to the Sheffield Royal Infirmary on March 3, 1958, with a history of dyspnœa and passage of dark urine for the past week, and of generalised œdema for forty-eight hours Anasarca and pulmonary congestion were confirmed, the blood-pressure was raised, and the urine contained albumin, red blood-cells and casts A throat swab prior to penicillin therapy grew commensals only The patient was treated by bed rest, restriction of protein, fluid, and salt intake, and systemic penicillin for fourteen days, followed by oral phenoxymethylpenicillin until her discharge on April 4 She was then symptom-free and the blood-pressure had returned to normal, but the urine still contained some albumin, red blood-cells, and occasional hyaline casts A week after returning home the patient had recurrence of acute tonsillitis, which was treated with oral penicillin When her condition was reviewed on April 18 a β-hæmolytic streptococcus was grown from a nasal swab

Case 2 —Her mother informed us that Joan's sister, Jane, had been admitted to the Sheffield Royal Hospital on April 5 with severe acute nephritis A throat swab taken after three days' penicillin therapy grew only mouth commensals Jane was treated with systemic penicillin for twenty-three days Further throat and nasal swabs on April 17 again failed to grow pathogens

Case 3 —The family doctor sent up a third daughter, Mary, who had developed hæmaturia and facial swelling a week previously A throat swab after admission (April 18) grew a β-hæmolytic streptococcus She received the same treatment for acute nephritis as case 1 and was discharged to a convalescent home on May 8

As soon as it was realised (April 18) that multiple cases of acute nephritis had occurred, the whole family was asked to attend (April 19) for further investigation The only abnormalities discovered were unilateral conjunctivitis in the mother (present for a month, complicating long-

FINDINGS IN Q FAMILY

Name	Age (yr)	Interval (weeks)*	Swabs		Clinical sequelæ
			Nose	Throat	
Joan	14	0	0 +	− −	Acute glomerulonephritis
Jane	15	3	0 −	− −	Acute glomerulonephritis
Mary	13	4	0 0	+ −	Acute glomerulonephritis
John	11	5	+ +	− +	None
Martha	8	5	+ +	− +	Symptomless albuminuria with red and white blood-cells *and cellular* casts in urine (April 19) Repeat urine examination showed trace of albumin, occasional red and white blood cells, *no* casts (May 1)
Francis	6	5	+ +	− +	None
Rose	3	5	+	−	None
Kenneth	1½	6	− −	− −	Cervical adenitis and otitis media (β-hæmolytic streptococcus, Lancefield Group A, Griffith type 1, isolated from aural discharge)
Mother	38	8	+ +	+ +	Monoarthritis (E S R *25 mm in* 1st hour, Wintrobe) Conjunctivitis complicating chronic nasolacrimal-duct obstruction (β hæmolytic streptococcus, Lancefield Group A, Griffith type 2, isolated from conjunctival sac)
Father	40	8	0 −	+ +	None
Harold	17	9	− +	− −	Polyarthritis (E S R 41 mm in 1st hour, Westergren Antistreptolysin titre 1 600)

* Figures refer to interval in weeks between onset of infection of upper respiratory tract in initial case (Joan, 1st week February, 1958) and subsequent cases

+ = β-hæmolytic streptococcus Lancefield group A Griffith type 1 isolated
− above organisms not isolated
0 no swabs taken

Swabs were taken from inpatients on admission and after an interval
Swabs were taken from outpatient attenders on April 19 and May 1

DR OPIE, DR SPALDING REFERENCES

Dornhorst A C , Leathart, G L (1952) *Lancet*, ii, 109
Engel S T (1947) The Child s Lung London
Fry, D L , Stead, W W , Ebert, R V , Lubin, R I , Wells, H S (1952) *J Lab clin Med* 40, 664
Lassen H C A (1953) *Lancet*, i, 37
Lilly, J L (1950) Methods in Medical Research vol 2, p 31 Chicago
Ross B B , Gramiak, R , Rahn H (1955) *J appl Physiol* 8 264
Russell W R , Schuster E Smith, A C , Spalding, J M K (1956) *Lancet*, i 539
Smith A C Spalding J M K , Russell, W R (1954) *ibid* i, 939
Spalding J M K Smith A C (1956) *ibid* ii, 1247
Werko L (1947) *Acta med Scand* suppl 193
Whittenberger J L (1957) *Int Poliomyelitis Conf*

standing nasolacrimal duct obstruction), an infected nose in Martha, and cervical adenitis with a discharging middle ear in Kenneth. The blood-pressure was measured in all except the two youngest children and was found to be normal. Non-catheter specimens of urine were normal in each case except that of Joan, who had been recently treated for acute nephritis and whose urine still contained some albumin and red-blood cells, and of Martha, whose urine contained a moderate amount of albumin, an excess of red blood-cells, occasional cellular casts, and leucocytes No other clinical evidence of acute nephritis was obtained in this girl and the urinary abnormality was thought to represent mild acute nephritis Throat and nasal swabs were taken from all those attending In addition the mother's conjunctival and Kenneth's aural discharges were cultured β-hæmolytic streptococci, Lancefield group A, were isolated from one or more sites in all those examined, except Harold.

On May 1 the family was visited at home We learned that Harold had developed pains in both ankles during the previous week, and was receiving physiotherapy at a clinic. On this occasion his throat swab grew a β-hæmolytic streptococcus, later found to be of Lancefield group A, Griffith type 1 His erythrocyte-sedimentation rate (E S R.) was 44 mm in the 1st hour (Westergren) and his anti-streptolysin titre was 600 Further throat and nasal swabs were taken in six of the others β-hæmolytic streptococci group A were again isolated from each except Kenneth The first β-hæmolytic streptococcus isolated from each subject was later typed in the Streptococcal Reference Laboratory, Colindale, through the courtesy of Dr R. E O Williams, and found to be of Griffith type 1, except the streptococcus from Mrs Q's conjunctival sac, which belonged to type 2 Blood was taken from cases 1–3 and their mother (May 30), and the sera were tested for type-specific antibodies In each case antibody against type-1 streptococcus was demonstrated, and there was a suggestion that the antibody was more active for the homologous strain than for a stock type-1 strain There was only slight activity with the sera from cases 1–3 against some type-12 strains—not strong enough to suggest that the nephritis was really due to an inapparent type-12 infection.

Discussion

We feel that this familial outbreak of upper-respiratory infection was caused by a type-1 streptococcus for the following reasons.

1 The organism was recovered from ten of the eleven members of the family within two to nine weeks of the individual initial throat infections

2 No other types of β-hæmolytic streptococci were isolated from a total of thirty-nine swabs with one exception that from Mrs Q's conjunctiva grew a type-2 streptococcus, but she also carried a type-1 in her nose and throat. Harold Q was the only member of the family whose swab failed to grow any streptococci on April 19, and he was the only one who had not by then contracted an infection of the upper respiratory tract. A few days before the second swabbing on May 1, which grew type 1 streptococcus, he contracted polyarthritis

3 Blood taken from cases 1–3 and from their mother (May 30) contained antibody to type-1 streptococcus

It has been appreciated for some years that, with few exceptions, the incidence of rheumatic fever following Lancefield group-A streptococcal infection is fairly low and that the attacks are not associated with any specific type (Siegel et al 1955) In contrast to this, the incidence of acute nephritis, following streptococcal infection varies considerably in different streptococcal outbreaks In recent years the bacteriology of community outbreaks of acute nephritis has been studied by typing the streptococci isolated from the upper respiratory tract. These studies have shown that in cases of acute nephritis certain types of streptococci are much more commonly isolated than other types Thus, types 4, 12, and 25 have been incriminated in various parts of the world. A hitherto undescribed type of streptococcus—Red Lake—has been added to the known "nephritogenic" types (Updyke et al 1955) Infection with other types, including type 1, have been associated only sporadically with acute nephritis In Great Britain Wilmers et al 1954 found that of 31 cases of acute glomerulonephritis, treated in various London and provincial hospitals, 28 grew type-12 streptococcus, while the remaining 3 grew types 1, 2, and 3 respectively In a concurrent investigation in which β-hæmolytic group-A streptococci from 1380 patients were typed, type 12 occurred in 8 2% and type 1 in 10%. They concluded that in Great Britain as in the United States acute glomerulonephritis was closely related to infection with type-12 streptococcus From their figures no such relationship is discernible for type-1 streptococcus in 1953

In a large outbreak of streptococcal illness in Wyoming type-1 streptococcus was isolated from 196 patients, but no cases of acute nephritis developed amongst these (Rammelkamp and Weaver 1953)

The Q family outbreak appears to be the first reported in which a high incidence of acute nephritis following type-1 streptococcal infection has been demonstrated Of the ten affected members of the family three contracted clinical acute nephritis, and a fourth had the urinary changes of acute nephritis without displaying symptoms This type of renal reaction to streptococcal infection has been described after scarlatina (Harries and Mitman 1947) It is of interest that two of the infected people contracted rheumatic arthritis

It seems likely that the high incidence of acute nephritis in this family following infection with type-1 streptococcus was at least partly due to a "nephritogenic" variant of type 1 This is suggested by the fact that the sera of the patients showed a more powerful bactericidal power against the strain of type-1 streptococcus, involved in this outbreak, than against a stock "non-nephritis" type-1 streptococcus

Summary

Four cases of acute glomerulonephritis were detected in one family, following infections of the upper respiratory tract with β-hæmolytic streptococcus group A, type 1

A distinct "nephritogenic" action has not previously been ascribed to the type-1 streptococcus

We thank Dr E W Skipper for permission to publish, Prof C H Stuart-Harris and Dr D Verel for access to the notes of case 2, and the family practitioner, Dr P W O Brien, for helpful information The streptococcal grouping was carried out in the departments of Dr J Colquhoun and Dr E H Gillespie, to whom we are grateful for criticism and advice We also thank Dr R E O Williams who kindly typed the organisms, demonstrated type-specific antibodies, and discussed the outbreak with us

REFERENCES

Harries, E. H. R., Mitman, M. (1947) Clinical Practice in Infectious Diseases Edinburgh
Rammelkamp, C. H., Jr, Weaver, R. S (1953) *J clin Invest* 32, 345
Siegel, A. C., Rammelkamp, C. H., Jr, Griffeath, H I (1955) *Pediatrics*, 15, 33
Updyke, E L, Moore, M. S., Conroy, E. (1955) *Science*, 121, 171
Wilmers, M J, Cunliffe, A. C., Williams, R. E. O (1954) *Lancet*, ii, 17

Reviews of Books

Scottish Social Welfare, 1864–1914

THOMAS FERGUSON, C B E , M D , F R C P E , professor of public health, University of Glasgow Edinburgh E & S Livingstone 1958 Pp 610 42s

THIS vast storehouse of information carries on the story begun in *The Dawn of Scottish Social Welfare,* published in 1948 If the later period differs from the earlier days in that its contrasts are less spectacular, the change which has overtaken social affairs since 1914 is still remarkable and no less remarkable is the change which has come over the public attitude to social problems Long and interesting chapters deal with general environment, housing, food, the relief of destitution, infectious diseases, the care of the sick, and the welfare of mothers and young people Particularly interesting are the changes in such varied communities as the city of Glasgow and the isolated crofters in distant islands In both places the housing problem was formidable and utterly different

To begin with, the education of the adult population of remote parts, especially in the Hebrides, did not improve rapidly, so far at least as capacity to sign marriage registers was concerned In Scotland as a whole, 10% of men and 20% of women signed by a mark in 1862 and 1872, and 7% and 14% respectively in 1881 Judged by this standard, much the most backward counties were Inverness and Ross and Cromarty, in Ross and Cromarty, 34% of men and 49% of women signed by the mark in 1862, 26% and 49% in 1872, and 24% and 47% in 1881 But the report of the Crofters' Commission in 1884 was able to claim that, while the educational level of adults in these counties was much below the Scottish average, the number of children being educated in that year was greater in proportion to population than in any other county except Caithness By 1910 the figures had fallen to 5%

Sekretionsstudien am Pankreas

Experimentelle und anatomische Pathologie DR VOLKER BECKER, Pathologisches Institut der Universitat Kiel Stuttgart Thieme 1957 Pp 119 DM 29 50

Dr Becker's monograph is a thorough attempt to correlate the histological features of the excretory tissue of the pancreas with the functional states produced in animal experiments Thus, the static picture of a histological section is identified with a definite stage in the disease process The results of ethionine-inhibited protein synthesis, of parasympathetic, splanchnic, and secretin stimulation, and of duct ligation, are described in laboratory animals killed at different intervals after the experiment began And work has also been concerned with the size and shape of secretory cells, distribution of zymogen granules, basal basophilia (as an expression of ribonucleic-acid content), size of nuclei, and distribution of chromatin and of nucleoli

Findings in human necropsy material are then described and interpreted on the basis of animal experiments 350 cases were studied, in 50 of which the necropsy was performed less than two hours after death Dyschylia, a secretion of abnormal fluid, and parachylia, an abnormal pathway of secretion, are terms used and discussed Reasons are examined for the belief that the dual secretions—parasympathetic-stimulated, rich in enzymes (proteochylia), and secretin-stimulated, alkali-rich and aqueous (hydrochylia)—have their morphological equivalent in an anatomical partition, the first being secreted by cells of the acinus, the second by cells of the isthmus

Some of Dr Becker's claims may be contested Thus, the increase in chlorides in the saliva in fibrocystic disease of the pancreas is explained by deficient dilution via duct cells, but the function of duct epithelium is water resorption against an osmotic gradient The strong reduction of tetrazolium salts by the duct epithelium, so conspicuous in the parotid and submaxillary glands, is wrongly attributed to pancreatic ducts also The role of postmortem autolysis is probably underestimated

Anyone interested in pancreatic disease will find the book useful and stimulating, and there is an exhaustive list of references

The Clinical Physiology of Physical Fitness and Rehabilitation

ERNEST JOKL, M D , professor and medical director, Rehabilitation Center, University of Kentucky Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1958 Pp 194 63s

THIS book is based on an essay for which the author was awarded the Buckston Browne prize and medal of the Harveian Society of London He suggests that, though medicine has made great advances in the past fifty years, these have been accomplished principally by utilising laboratory and experimental methods, to the detriment of the art of clinical observation In the present work he seeks to redress the balance, pointing out that the worker in physical medicine and rehabilitation is ideally placed to develop new clinical techniques

One obstacle is that the scientific basis of rehabilitation is still only vaguely defined Indeed, the realisation that rest alone will not always suffice for the optimum recovery of the body from a disease process, is comparatively recent Dr Jokl elaborates the thesis of Julius Cohnheim and William H Welch that "the healing power of nature is frequently incomplete and imperfect" by describing instances in which dissatisfaction at the results yielded by this natural power, operating alone, led to high and imaginative standards in rehabilitation Such standards have sometimes resulted in almost incredible accomplishments (for example, the world record in hammer-throwing was, in 1956, held by a man whose left arm was almost totally paralysed)

This book can profitably be examined from several different angles It is a monograph in physiological research, reporting original work on the prognostic significance of the ballistocardiogram It is a study of the recent history of physiology, embodying a series of short, but attractively illustrated, biographies of such figures as Sir Charles Bell, Hughlings Jackson, and Amand Duchenne Finally, the case-histories it embodies constitute intriguing and stimulating examples of the remarkable standards of recovery which are, on occasion, attainable even by the seriously handicapped

An Atlas Concerning Morphological Aspects of Visceral Nerve Endings

Contribution to the Study of the Problem of Interoceptors Prof DR I NICULESCU, M D , corresponding member of the Rumanian Academy of Sciences Bucharest Editura Medicala 1958 Pp 455

THIS work appeared some months after the death of its distinguished author The text amounts to only 30 pages, but it is repeated in several languages, including English It includes a useful section on the intraneuraxial pathways of the interoceptors and proprioceptors, and a short account of the cortical representation of vegetative functions The many drawings illustrating nerve-endings in various laboratory animals are mostly in two or three colours and are very clear Methylene-blue and carmine appears to be his method of choice for fresh impregnation, but use is also made of various standard silver techniques One illustration shows the autonomic microganglia of the subserous layer of the human fœtal bladder, which is so rich in synaptic structures

Eden and Holland's Manual of Obstetrics (11th ed London J & A Churchill 1957 Pp 751 63s)—In the latest edition of this classic Mr Alan Brews provides a comprehensive and easily read account of current obstetric practice It is profusely illustrated with excellent diagrams and plates There is little emphasis on manipulative and operative obstetrics, which is proper in a book intended primarily for the undergraduate In spite of claims to the contrary the M R C O G candidate will be obliged to read more widely obstetric anæsthesia is only briefly considered, Kielland forceps get half a page, pudendal-nerve block is just mentioned, Lovset's manœuvre is not described, and the account of the management of breech delivery is not fully up to date Nevertheless, the book can be thoroughly recommended to the undergraduate, and the general practitioner will find in it a sound answer to every unusual obstetric problem

THE LANCET

LONDON 27 SEPTEMBER 1958

Resources for Research

THOSE who visit American medical schools are impressed by the amount of money at their disposal for medical research. Last year the grant from Federal funds alone was $186 million; industry contributed $90 million, charitable foundations earmarked $35 million for specific projects, and further substantial sums came from local collections (e.g., "Heart Sunday") and sums allotted by individual States to their universities. The municipality of New York has just set up its own Health Research Council with an initial appropriation of $600,000 and a possible eventual budget of $8 million a year (see p. 702). Congress has now been told by a special committee that it is not putting enough money into medical research and that $1000 million annually should be spent by 1970.[1] Yet already Congress is putting into research twenty times the budget of our Medical Research Council. This vast endeavour is exemplified in the National Institutes of Health at Bethesda with 6000 medical and ancillary staff. In the U.S.A. all avenues into medical research are wide open, and there are splendid facilities even at the student stage. Hospital consultant staffs are far larger than ours, and at every grade each member is expected to contribute actively to the development of ideas in medicine. Dr. SMYTHIES' article on p. 689 of this issue graphically underlines the prominence of research in American thought. In our more strictly selective system, necessitated by relative poverty of money and facilities, many American investigators would hardly have had a chance. By full deployment of their talent, and by the efforts of great numbers, an immensely rich soil is being developed from which new research ideas can be harvested.

When new scientific approaches originate in this country they may be elaborated all too slowly by "one man and a boy" working in cramped space with makeshift equipment, whereas in the United States large teams at once get to work on every promising idea. Consequently we have depended on the United States for the development of new antibiotics, and to the United States, too, must go full credit for most of the progress in protection against poliomyelitis. These are advances well known to the man in the street, but far more important is the ferment of new biological ideas from which other discoveries will spring. Fundamental biological and physiological science in the U.S.A. is closely integrated with clinical research, and extensive laboratories are available not only to the basic medical scientists but also to clinicians for studying problems arising out of human disease. By contrast, medical research in this country is undergoing relative attrition despite an expanding economy. In the universities new building for medical and biological sciences is much more restricted than that for physical and technological subjects. There is no surgical animal research laboratory in any English university—though one is now nearing completion. There have been no new teaching hospitals in this country since the 1939–45 war, so even the application of the new methods developed here or elsewhere is frustrated or difficult. Careers in basic medical science have become unattractive in salary and prospects compared to the glamour of consultant medicine—once achieved. The young clinical trainee who engages in research is often terrified that he will thereby become labelled a "laboratory man" (derogatory only in this country) or too specialised for the next vacancy in a provincial hospital. The real gravity of our situation is underlined by the fact that some of our research directors and medical professors, as well as promising younger investigators, are leaving this country to work on the other side of the Atlantic, where they find that, in their laboratory and investigative work, they are given encouragement, lavish support, and almost unlimited opportunity. This is happening even though adaptation to the American way of life may be none too easy for the expatriate of mature years.

We may claim that, because of the very restriction of opportunities, there is a more concentrated selection of ability in British medicine—that in American medical research, as in the American economy, there is much waste. Our professional leaders are in fact very highly selected, but if the scientific training of our young men continues to be discouraged our leaders will be selected from a dwindling field of applicants. Already our medical faculties often find great difficulty in filling their professorial chairs. We justly pride ourselves that under the N.H.S. there are more specialists than ever before, but we should not pretend that this growth in specialist services will by itself keep British medicine in the forefront. We cannot maintain our standards without the vigorous pursuit of research in our medical schools, for even good routine will decline without the stimulus of critical thought engendered by investigative work. Scholarship alone—meaning the study of other people's thoughts—can never keep a profession alive. It failed in the Middle Ages and it would fail again now.

With our smaller population and national income we naturally cannot spend as much money on research as the United States. But we could with advantage spend more than we do, and we should make sure that our resources are used with imagination. Poverty need not make us too despondent, or proud, to learn from the American system such useful lessons as the encouragement of research among all branches of the profession, including students. The clinical prizes offered by some regional hospital boards and the more ambitious studies being made by the College of General Practitioners recognise this need. Again, though we cannot compete with the generosity of American industry and trusts, we could perhaps foster a new age of patronage. Lord Nuffield has already shown us the way, two of the royal colleges have lately received princely gifts for research, and the Mental Health Research Fund, which supports some investigations into the problems Dr SMYTHIES mentions, offers an opportunity for ordinary citizens to make small contributions

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[1] *N.Y. Times*, July 14, 1958.

Our Commonwealth links no longer depend on the strength of our military force, but on our scientific, cultural, and commercial leadership (Many of us can remember the uplift to the national pride and prestige of Canada which followed the discovery of insulin) Supported by the basic disciplines of physiology, biochemistry, and microbiology, which in turn utilise techniques of physics and chemistry, medical science is a part of general science Progress in one science inevitably impinges on all associated branches Uneven progress of science is impossible, and thus the present policy of preferential development of the physical sciences seems to be utterly faulty In the U S S R, where the academician holds the highest place in society, there are signs of an intensified application of basic sciences to medical problems In this country we have no lack of talent, but without more financial encouragement, more laboratories, and more facilities for research, we shall lose our best workers, and gradually the standards of medicine even at a practical level will decline

First Responses to Local Infection

How primary bacterial infections may in nature be limited to the site in which the organisms first lodge and multiply is still unknown Although hyperæmia, heat, swelling, suppuration, and healing follow primary infections and are known to be due in sequence to to dilatation of blood-vessels, increased blood-flow, œdema, and diapedesis of leucocytes, then regression of these dynamic events, and finally scarring, their relation in time to the death and restricted spread of bacteria is still open to question Direct visual observations of these events in response to injury in transparent tissues have usually been made using chemical or physical agents with limited action whose extent depends on the dose Yet even with these it cannot be judged when the stimulus to the response ends and the consequences of the response begin The problem of these time-sequences is increased with living micro-organisms through their own capacity to multiply and produce injurious substances which in their turn damage the tissues chemically Thus an infection with living bacteria will be limited and localised only if the bacteria are prevented from escaping and are killed on the spot On the spot or nearby are phagocytes and their potential progenitors which can kill bacteria, and destructive antibody may be generated locally and possibly rapidly In vascular tissues both cellular and humoral antagonists are brought to the site by the blood-stream Though the possibility of local destruction of bacteria in non-vascular regions has long been known, it has usually been assumed that blood-borne phagocytes and non-specific immune substances are decisive in limiting infection in vascular tissues Localisation has been attributed by some to thrombotic plugs in efferent blood and lymphatic vessels The decisive factors limiting infection will be those which first kill infecting bacteria Thus the time after infection at which these are all dead or so greatly decreased as to be ineffective must first be known before the manner of their death can be determined A decision to investigate local events in the first five hours after the infections which were known to remain localised was arrived at by BURKE and MILES [1] on the basis of much previous experience of MILES and his coworkers [2-4] using enhancement of infectivity to judge the time when most of the bacteria were killed

Inflammatory lesions of a standard size were obtained consistently at twenty-four hours after injections of suspensions of known bacterial content To produce a final lesion of the same size different numbers of bacterial cells were required for different micro-organisms Experience showed that the size of the definitive lesion could be modified much by various enhancing agents When these were injected within three to four hours after primary infection the size of the twenty-four-hour lesion was increased The enhancing agents were adrenaline, general shock, and liquoid (an inhibitor of complement) The degree of enhancement was measured as increase in lesion size, and it could be interpreted as equivalent and proportional to an increase in the number of bacteria of the primary infection Enhancement occurred, however, only when attempted within three to four hours after primary infection From these observations it was concluded that after the first few hours the bacteria were either dead or so greatly diminished as to be incapable of responding by further damaging action to the favourable conditions afforded by enhancers The death-rate of bacteria was estimated at 50–99 9% in the first two hours of infection In a further paper MILES and MILES [5] have described a method of making bacterial counts in fresh tissues

Having found a decisive period within which both lesion size and localisation were determined for a given dose, BURKE and MILES [1] investigated the sequence of events in early infective inflammation Increased permeability (measured by dyeing with intravenous pontamine sky blue), increased stickiness of capillary endothelium (demonstrated with intravenous saccharated iron oxide), and tissue leucocytosis (estimated in stained sections) were used as criteria and measures of inflammatory response Capillary dilatation and œdema are not amenable to accurate measurement, though both are more directly representative of response Nine different infective agents, including one, *Streptococcus pyogenes*, isolated from a natural guineapig infection, were used to obtain lesions of a standard size of 10 mm in twenty-four hours In 6 of these the time-relations of vascular reactions were similar In the first two hours of the decisive period macroscopic signs of inflammation were scanty, they did not become obvious until the third or fourth hour, and they were not fully developed for several hours Capillary permeability, measured by the extent and depth of staining in the region around injected bacteria, increased transiently in the first half-hour, and subsequently there was a larger increase with a maximum at three to four hours In this second phase œdema and microscopically detectable leucocytosis increased Yet later, after the fifth hour, when induration and leucocytosis continued to increase, there was low permeability to the dye This observation causes Burke and Miles to suggest that the relation of vascular permeability phenomena to effective defence against local infection should be re-examined Of all the terms used, induration is left least defined If there is indeed "hardening", this is more than simple œdema In a previous publication Miles et al[4] stated that no fibrin could be demonstrated outside the central area which was destined to undergo coagulation necrosis Thus it seems that only the accumulation of phagocytes can account for this change in texture Great insight into the manner of dye diffusion along fibres and into œdema fluid has been provided by McMaster and Parsons[6] Their methods of observation may help to explain why dye no longer escapes while œdema fluid and leucocytes collect and the whole lesion becomes hardened During this early period there was no evidence of thrombosis of blood or lymphatic vessels

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[1] Burke, J F Miles, A A *J Path Bact* 1958, 76 1
[2] Evans, D G, Miles, A A, Niven, J S F *Brit J exp Path* 1948, 29, 20
[3] Miles, A A, Niven, J S F *ibid* 1950, 31 73
[4] Miles, A A, Miles, E, Burke J *ibid* 1957, 38, 79
[5] Miles, A A, Miles, E *J Path Bact* 1958, 76, 21

To what extent can these findings be applied to natural infection? In the experimental infections the pathogenicity of the microorganisms used might be questioned, and Burke and Miles imply, and in one instance Miles and Miles[5] state, that with larger bacterial doses spreading and generalised infections occurred even in the absence of enhancers The particular example of systemic infection was seen with *Str pyogenes*[7,8] which had been isolated from a natural guineapig infection This essential piece of evidence removes two further objections to the realism of the experiments All the organisms, including the streptococci, had been frozen, dried, stored, and washed with distilled water before use. Several million were injected to represent an infecting dose, and they were introduced intradermally in a stabilising suspension which formed a small bleb about 1 mm in diameter How the suspension compares quantitatively with natural infection might be estimated Conditions inside a bleb are described, and further information on the situation may be gained from the revealing observations of S H Bensley[9]

The many observations now assembled indicate that the decisive period in which infection is limited precedes the classical early signs of acute inflammation in vascular tissues, and suggest that these early signs are responses to the aftermath of infection The versatility displayed in this series of publication should enable those taking part to proceed to the even more difficult task of detecting early unseen agents of bacterial destruction

Papa Virchow

As part of its autumn meeting in London, the Association of Clinical Pathologists is celebrating on Oct 3 the centenary of the publication of Virchow's *Die Cellularpathologie* with a symposium on the pathology of the cell, to be opened by Sir Roy Cameron with a paper briefly entitled "1858" It is an event well worth celebrating

Modern biology, after some centuries of irregular acceleration and many false starts, may fairly be claimed to have been launched on its tumultuous career with the publication in three successive years of three of the most seminal works of the whole scientific canon—Pasteur's *Memoire sur la fermentation appelée lactique* in 1857, *Die Cellularpathologie* in 1858, and *The Origin of Species* in 1859 It is easy to think of Virchow's work as important only as the well-head (with Morgagni's *De Sedibus*) of pathology, but it is a great deal more than that It established the cell as—after the body-as-a-whole—the prime unit of investigation, not only for medicine, but for biology in general Cells were of course not invented by Virchow The word is as old as Hooke's pioneer microscopic description of cork in 1665 The idea that living matter is characteristically divided into separate units, each with a nucleus, stemmed largely from the work twenty years earlier of Schleiden, Schwann, and Muller, and, in the descriptive sense at least, had already been greatly developed by Kolliker and Remak But Virchow added two major contributions to the "cell-theory" In the first place, he is responsible for one of the great biological generalisations—*Omnis cellula e cellule* By something more than coincidence, the core of all three of these near-contemporaneous works is their demonstration, on three very different planes, of the continuity of living matter Darwin destroyed separate creation, and showed that all species stem from a single family tree, Pasteur destroyed spontaneous generation, and showed that his "ferments", which were microorganisms, came from preexisting living matter, Virchow destroyed the idea that cells were a mere local crystallisation of protoplasm from an undifferentiated continuum, and showed that every cell resulted from the division of another cell In the second place Virchow established the "cell-theory" by showing that it had practical use The sharp realities of medical practice afford the sternest test and, if successful, the most brilliant vindication of any biological theory The cell-theory made it possible to understand the appearances presented by diseased tissues under the microscope, and added a new dimension to pathology (some day the electron-microscope will find its Virchow it is still in the Hooke stage) Though his techniques for the preparation of sections were primitive —paraffin embedding and most of our standard stains were at least a decade away—he launched the science of histopathology The enormous increase in accuracy of prognosis possible (in the case of tumours especially) by the use of microscopic methods based on Virchow's ideas supplied the best possible proof of their validity

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[6] McMaster, P D, Parsons, R J *J exp Med* 1939, 69, 247, 265

[7] Miles, A A *in* Lectures on the Scientific Basis of Medicine, vol 3, p 235 London, 1955

[8] Dutton, A A C *Brit J exp Path* 1955, 36, 128

[9] Bensley, S H *Anat Rec* 1934, 60, 93

It is sad that most have heard of VIRCHOW as a diagnostic histopathologist only in the matter of the Emperor FREDERICK III, his misdiagnosis as benign of the biopsy taken by MORELL MACKENZIE from the Emperor's laryngeal carcinoma was one of the more distressing factors in that most distressing case Yet we may remember that even today this can be a difficult diagnosis, and that MACKENZIE, working with a mirror and no anæsthetic, may well have missed the real tumour Moreover, though it ruined MACKENZIE, the mistake was probably for the good of the patient, who would have been subjected otherwise to a laryngectomy, the mortality of which at the time was at least 75% In any case, before *Die Cellularpathologie* there would have been no biopsy VIRCHOW in fact made many mistakes Beside his brilliant elucidation of the cellular nature of leukæmia and of sarcoma there stands, for instance, a detailed account of the origin of carcinoma from the cells lining lymphatic channels But it is for his achievements rather than his mistakes that he is to be remembered And they were innumerable For fifty years he was the leading figure in German pathology, and this was a time when German pathology far outstripped that of the rest of the world He was in addition very many other things—anthropologist, archæologist, hygienist, politician His famous *Archiv*, founded in 1847 when he was 26, and still one of the world's leading medical journals, contains in its earlier volumes many contributions on subjects far removed from pathology

He remains even today the father figure of pathologists the world over He established the microscope as an essential tool of medical research and of medical practice He established pathology as an independent discipline, occupying the vantage point of a middle ground between the ivory tower of pure science and the clinical hurly-burly of pure application If today the average pathologist seems to have rather diverse interests, concerning himself with the blood-groups of the Aztecs one month and the hospital drains the next, he—and with him the whole profession and its patients—owes more than he generally realises to the example of Papa VIRCHOW

Annotations

LAYMAN'S AID

FOR eighty years the Order of St John of Jerusalem, through its Ambulance Association, has produced manuals for the instruction of the layman in the immediate management of injuries and sudden illness For almost as long the St Andrew's Ambulance Association and the British Red Cross Society have had similar textbooks This year their common aims and practices have had their obvious consummation in the production of a joint manual, simply titled *First Aid* [1] Nearly all accidents and sudden illnesses are seen and treated first by a layman, and people keen to help their fellows turn to accidents and illnesses as an obvious opportunity to serve Policemen, firemen, railwaymen, and pitmen, engaged in hazardous work, voluntary institutions whose members attend public meetings, young men and women who climb mountains or fly, and indeed anyone who takes his car out of the garage, may be the first to see someone suffer injury, or may suffer one himself The doctor who tries to repair the damage often appears late in the succession of those who have contributed in some way to its treatment

It is part of the system of training first-aiders that advice shall be simple, clear, and dogmatic Hesitancies must be suppressed, and every dilemma must be resolved before instructions on first-aid are laid down This book will be the ultimate authority for many people for many years to come

The first and perhaps the greatest dilemma facing the authors of such a book is between simplicity and comprehensiveness A simple manual reaches a wider public, and, because first-aid is needed widely, some would say the barest minimum of information will do the greatest good This argument influenced the Priory of Canada when they published *Fundamentals of First Aid* [2] three years ago In this book Dr Robert A Mustard discarded all discussion of shock, and all description of pressure-points He condemned the tourniquet outright as a first-aid instrument, discouraged the use of bandages to stabilise fractures of collar-bone, jaw, ribs, pelvis, and some others, and in many other ways shortened the course and limited the exercises which have been practised throughout this country for generations Our own book, on the contrary, contains more material than it did thirty years ago, although its size, because of streamlining and simplification, is not much increased It prefers comprehensiveness, encourages the maintenance of a corps d'élite, aims particularly at the team which trains diligently, and fosters the cult of first-aid training by devoting, for instance, eighteen pages to stretcher exercises

Yet in many ways this new book brings the practice much closer to modern conditions Although sections on civil defence and labelling of casualties in war might indicate that it is becoming more complicated, the improvement in communications, hospital services, and medical care make the first-aider's task easier under our present organisation Elaborate splinting of fractures may not be necessary if a hospital is near, and we are warned not to delay disposal of a casualty by work which is to be undone a few minutes later Experts in first-aid will still argue over occasional details Holger-Neilsen takes definite priority over Schafer in artificial respiration, though both methods are well described We are still to transport the patient with a fractured spine on his back, though an appendix instructs on the prone position "if it is unavoidable" Every casualty officer will have sympathy with the first-aider who is being coached in differentiation between twelve or more listed causes of unconsciousness

Dr L S Potter's editing has had much excellent writing to draw on from previous editions, but we detect a new and vivid pen in places "the whole spine is *strapped together* [our italics] by bands of strong fibrous tissue" Every medical student might well prepare himself for more detailed studies by reading the simple survey of human anatomy and physiology at the beginning This work is, of course, not intended primarily for doctors, though no doctor would lose by studying it *Many* thousands serve the ends to which doctors are dedicated, and it is here to serve them The ancient Hospitallers of St John and their kindred brotherhood the Templars (whose seal showed two knights upon one horse) would have approved this combination of forces in a single vehicle, in pursuit of a single aim

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[1] First Aid the authorised manual of the St John Ambulance Association, the St Andrew s Ambulance Association and The British Red Cross Society 1958 4s

[2] Fundamentals of First Aid By Robert A Mustard Published and approved by the Priory of Canada of the Order of St John, 1955

THE COMMON COLD

IN this coming season of mists and mellow fruitfulness our thoughts turn once more to influenza and the common cold After last year's bumper harvest the influenza virus may decide that the soil is too heavily immunised But that hardy old perennial, the common cold, is unlikely to give us any peace, and as the schools open, we can expect it back again

Dingle[1] gives us a timely reminder of our ignorance of the subject in his presidential address to the American Association of Immunologists In a group studied by Hope-Simpson,[2] each person has on average 7 colds a year, and therefore spends practically one day out of every five coughing and sneezing Many of us will react to this by protesting that we hardly ever catch cold, and we will support this by describing our favourite prophylactic or remedy If so, we shall be doing just what Dingle says we shall do, because ignorance of the cause, predisposing factors, and treatment of the common cold is so great that the field is wide open for theories and unproven assertions One of the commonest—that colds are caused by chilling—is beginning to weaken under constant experimental attack, and it now seems clear that a feeling of chilliness is often an early symptom of infection rather than a causal or predisposing factor But it may take some decades before the public are persuaded of this Dingle also emphasises our ignorance of the methods of natural transmission of colds and of factors of resistance and susceptibility Psychological factors in resistance to colds are now being invoked, and, if this seems an unlikely association to some, it is worth reflecting that Dingle was himself responsible for a most careful trial from which it emerged that, three weeks after having been infected with a common-cold filtrate, volunteers showed no specific immunity to the same virus Attack-rates are higher in children and tend to decrease with age, but it is not yet established whether this reflects increasing immunity or diminishing exposure to virus

If the disease is full of puzzles, the virology, according to Andrewes in a De Lemar lecture,[3] is not without its problems New techniques of virus isolation and study continue to reveal more and more viruses, and often the biological characters of the virus are known in some detail before its epidemiological significance is understood Besides the influenza viruses and adenoviruses, new viruses are being recovered every few months from people with upper-respiratory disease of one kind or another The question arises whether new pathogens are being discovered, or whether we are just beginning to amass a collection of relatively harmless virus commensals which correspond to the bacterial commensals isolated in the first flush of enthusiasm for detailed bacteriological investigations So far none of the viruses isolated has shown a clear association with common colds, but Andrewes nevertheless raises the question whether the common cold will be found to be a fairly common response to infection with a large number of different viruses, or alternatively where there is a single common-cold virus Until now, attempts at continuous cultivation of it (or them) in the laboratory have not proved successful In this phase of rapid advances it will be surprising if the common-cold virus resists cultivation for very much longer—although, even if the virus gives in quite soon, we may still spend many years wearing our flannel underwear to keep off chills Meanwhile it is noteworthy that Dr J Morrison Ritchie, whose latest report appears on p 699 of this issue, has confirmed his earlier observation that full development of a cold can often be prevented by administration of an antibiotic at the onset

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1 Dingle J H. *J Immunol* 1958, 81, 91
2 Hope-Simpson, R. E. *Proc R Soc Med* 1958, 51, 267
3 Andrewes, C. H *Bull Johns Hopk Hosp* 1958, 103, 1

POSTNECROTIC CIRRHOSIS

EVER since 1895, when Marchand[1] first described the development of nodular hyperplasia of the liver after an attack of acute yellow atrophy, the relation of this nodular lesion to other forms of cirrhosis has been disputed Lichtman[2] has been outstanding among those who refuse to regard it as an example of true hepatic cirrhosis, on the grounds that progressive replacement of parenchymal cells by scar tissue is the essence of true cirrhosis and the nodular hyperplasia that follows massive hepatic necrosis seems to represent the static end-result of a single acute episode On the other hand, Mallory,[3] Karsner,[4] and many others have long regarded nodular hyperplasia as a true cirrhosis, to which the term postnecrotic cirrhosis is usually applied Delay in resolving this difference of opinion has been due to many factors, but principally to the relative rarity of the condition and to our ignorance of the ætiology of almost all forms of hepatic cirrhosis Now a study by MacDonald and Mallory[5] of the 221 cases of postnecrotic cirrhosis that came to necropsy at the Boston City Hospital between 1917 and 1956 has provided convincing evidence that the disease is progressive

Unfortunately, this study throws little fresh light on ætiology Exposure to known liver poisons was negligible Malnutrition apparently played only a minor role, since nutrition could be regarded as adequate in over half the patients, but in 41% chronic alcoholism was a feature The outstanding result of the analysis of the case-records was the possible association with virus hepatitis No less than 24% gave a history of a previous attack of hepatitis or jaundice, and a further 44% had received multiple parenteral injections for one reason or another, thus exposing themselves to the risk of homologous-serum hepatitis But even in the former group, in only a third of the patients was the relation of the cirrhosis to the clinical attack of hepatitis reasonably direct In the other two-thirds there was an average interval of over fifteen years between the earlier attacks of jaundice and the appearance of symptoms unequivocally associated with cirrhosis The only justifiable conclusion from these data is that viral hepatitis is the most likely agent responsible for the majority of cases of postnecrotic cirrhosis, and the undoubted increase in incidence of this type of cirrhosis in recent years harmonises with this conclusion Yet it is not easy to understand why clinical manifestations of cirrhosis appear so long after the hepatitis Possibly the virus persists through the intervening years, causing slowly progressive damage that eventually emerges above the clinical threshold with hæmatemesis or ascites, or

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1 Marchand, F *Ziegler's Beitr path Anat* 1895, 17, 206
2 Lichtman, S S *Diseases of the Liver, Gallbladder and Bile Ducts*, vol I Philadelphia, 1953
3 Mallory, F B *New Engl J Med* 1932, 206, 1231
4 Karsner, H T *Amer J clin Path* 1943, 13, 569
5 MacDonald, R. A , Mallory, G K *Amer J Med* 1958, 24, 334

else the virus persists for months or years without producing any damage until, owing to some change in host-virus relationship, progressive necrosis of the infected liver cells occurs and leads to progressive cirrhosis A third possibility has been suggested if the initial damage produced were severe enough the resultant scarring might lead to vascular disturbances within the liver and thus to further necrosis and scarring Glynn[6] suggested a similar sequence to explain the irreversible stage of cirrhosis in rats that have received twice-weekly injections of carbon tetrachloride[7]

The ætiology and pathogenesis of postnecrotic cirrhosis are still far from clear As MacDonald and Mallory point out, the main impediment is the failure at present to reproduce virus hepatitis in an animal other than man Success here could lead to rapid progress in our understanding of postnecrotic cirrhosis

CHORIONCARCINOMA AN IMMUNOLOGICAL APPROACH

Because the immune processes in the causation of hæmolytic disease of the newborn have been determined, it is now possible to await its occurrence with some confidence and to set in motion the necessary treatment at the moment of choice Just under two years ago it was shown that Hashimoto's disease of the thyroid gland was caused by a cellular antibody reaction to leakage of thyroglobulin out of the thyroid acini[8]

This year a first attempt has been made[9] to apply the knowledge gained by P B Medawar and his associates in relation to tissue immunisation to the treatment of chorioncarcinoma Even though the degree of success in this particular patient is hardly capable of scientific interpretation, because many additional treatments were employed, the ideas which underlay the attempt can be applied to other patients and could lead to a revolution in approach to this dramatic and distressing tumour

The tissues of a mother and a child are not compatible, a skin graft from child to mother behaves as a homograft, not an autograft, because of the presence of paternal antigens in the cells of the graft Since chorioncarcinoma originates from fœtal tissue, half the genes in its cells are derived from the father Doniach et al considered, therefore, that deliberate immunisation of a patient suffering from chorioncarcinoma by her husband's cells might induce or enhance her tissue incompatibility (homograft immunity) towards cells containing the husband's genes and might thereby check or even destroy the tumour Immunisation was induced by intradermal or subcutaneous injection of white blood-cells from the husband on eleven occasions The earliest injections produced an immediate local reaction which subsided within a week The patient was tested by two means in an attempt to demonstrate tissue immunity to the husband's white blood-cells Firstly, skin grafts were made from the patient, her husband, and another donor The autograft survived but the two homografts disintegrated —the husband's more rapidly than the donor's Secondly, leucoagglutinins were demonstrated to a titre of 1 in 64 against the husband's white blood-cells These facts were regarded as evidence that immunity had developed in the patient against her husband's cells

During and after the period of immunisation and testing, the patient, who had had hysterectomy for proved chorioncarcinoma, developed vaginal recurrence and lung metastases, both of which were treated by deep X-ray therapy, with temporary improvement When extension of the pulmonary metastases was observed, four courses of treatment with an anti-folic-acid preparation were instituted, subsequently the lung shadows disappeared, and the symptoms were dispelled This was two years after the start of symptoms Doniach et al consider that immunity may have helped the action of the anti-folic-acid drug

Theoretically, it is to be expected that the very presence in the mother's uterus of chorionic cells, half of whose genes are derived from the father, will normally evoke a maternal tissue immune reaction which might check or modify their growth Possibly, when chorioncarcinoma develops and spreads, this mechanism is lacking or in some way modified Where the tumour spreads and spontaneously regresses, as it does in some cases, immunity may develop late or some kind of blocking mechanism may operate temporarily There are "infinite gradations of antigenic relations between the components of different tissues and different species"[10] There is clearly scope for further experimental study of these relations in chorioncarcinoma

DEFINING OVULATION-TIME

From America comes the suggestion that the time of ovulation can be simply and accurately pinpointed by the use of strips of tape or paper impregnated with the enzyme glucose oxidase, which, when placed against the cervix, will demonstrate by change of colour from yellow to green the increase in glucose content of cervical mucus known to occur at the time of ovulation Some physicians require the patient to visit the office daily for several days about the time when ovulation is expected[10] 'Tes Tape' is applied to the mucus cascade and the colour change in the tape is noted What happens, or should happen, when ovulation is imminent or has just occurred, is a change of colour to brilliant green and later to a darker green, indicating that coitus in the next 12 hours is likely to prove fruitful Doyle[11] of Boston, thinks that the tes tape can equally well be applied by the patient herself, using a cylindrical cardboard tampon The woman inserts one of these for a few minutes daily from the 8th to the 16th day of the cycle, and, unless she is colour-blind, can see when the colour changes to green She and her husband can then take appropriate action according to whether they want conception to occur or not Correlation of these colour changes with other ovulation indicators (shift in basal temperature, *Spinnbarkeit*, positive palm-leaf reaction, secretory change in endometrium) has been established Doyle has gone further and has demonstrated by colpotomy and at laparotomy the presence of a recently ruptured follicle and the production of a similar green colouration of tes tape dipped in spilled follicular fluid recovered from the pelvic peritoneum[12]

The efficacy of this new method of dating ovulation can be confirmed only by trials on many volunteers *If further experience* shows it to be accurate it should prove of value not only in the treatment of infertility, but also to those who practise the *rhythm* method of birth control

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[6] Glynn, L E *in Liver Disease a Ciba Foundation symposium*, p 74 London, 1951

[7] Cameron, G R, Karunaratne, W A E *J Path Bact* 1936 42, 1

[8] Roitt, L M, Doniach, D, Campbell, P N, Hudson, R V *Lancet*, 1956, ii, 820

[9] Doniach, I, Crookston, J H, Cope, T I *J Obstet Gynæc, Brit Emp* 1958, 65, 553

[10] Burnet, F M Enzyme, Antigen and Virus, p 106 London, 1956

[11] Birnberg, C H., Kurzrok, R, Laufer, A *J Amer med Ass* 1958, 166, 1174

[12] Doyle, J B *ibid* 1958, 167, 1464

Special Articles

A TRIPLET PREGNANCY WITH CRANIOPAGUS TWINS

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We report some preliminary details of a case of craniopagus twins Two features believed to be unique are that the mother gave birth to one single normal healthy baby at the same time as the conjoined twins and that one of the conjoined twins has had congenital hypertrophic pyloric stenosis The last case known to have been born in England was described in *The Lancet* exactly thirty years ago by Cameron (1928)

Craniopagus twins are the rarest of all conjoined twins, estimated at 1 in every 2 to 4 million births by Robertson (1953), who analysed Tartuffi's figures Of 117 conjoined twins 86 were joined anteriorly by the thorax (thoracopagus), 22 posteriorly in the sacral area (pygopagus), 7 caudally by the lower abomen (ischiopagus), and only 2 by the skull (craniopagus) The present case is the 42nd to be recorded in the available literature, but the 6th since 1949, which may reflect no more than the present age's greater ability to read and write

The usual fate of these babies has been death, sometimes in the first week, nearly always by the end of the first year One set, the first on record, 2 girls joined by the forehead born in Bierstadt in 1495 (Münster 1559), lived until the age of ten years, when one died The dead partner was cut away and the second died shortly after

In Cameron's case an emergency separation was attempted by Mr L Bromley on the twelfth day because one was obviously deteriorating, but both died during the operation Cameron commented that if the intradural spaces communicate, attempts at separation are useless Technical progress in neurosurgery, plastic surgery, and anaesthetics has altered the prognosis to some extent

The first success was reported by Sugar and Grossman in 1953 One baby died one hour after separation, but the other survived and was developing well at eighteen months Voris et al (1957) reported successful separation with satisfactory condition of both twins at two years and four months These three sets resemble in the photographs the set reported here, the main junction being between the parietal bones (c parietalis) The most recent paper, by Baldwin and Dekaban (1958), concerns craniopagus twins joined mainly at the forehead (c frontalis), a rarer type in which the actual area of the junction is smaller The twins were successfully separated in 1956 and both were within the normal range on their first birthday

Separation with survival of both of the twins can be successful only if sufficient tissue is present for two separate individuals The smaller the area of fusion the better the outlook. The tissues involved are the brain which has been adequate and virtually separate in hitherto reported cases The covering membranes, especially the dura mater, are usually deficient over some part of the fused area The arteries are expected to be independent, but the exact state of affairs must be established by angiography The most probable stumbling-block is large venous communication. Skin to cover the vertex can be prepared without great difficulty The problem of the replacement of skull bones has not yet been solved In only two cases so far reported have both of craniopagus twins survived (Voris et al 1957, Baldwin and Dekaban 1958), in Sugar's case (Grossman et al 1953), where there was a closer fusion, a common sagittal sinus made survival of both impossible, and from the description this case resembles the present one most closely.

Case-record

Obstetric History

The mother attended hospital for her fourth pregnancy after ten weeks' amenorrhœa. She was a healthy woman with a childhood history of scarlet fever, measles, and mumps, both she and her husband are of European descent Her first pregnancy had resulted in an abortion Two years later she was delivered by forceps at the forty-third week of pregnancy of a stillborn female infant weighing 3670 g (8 lb 1$^1/_2$ oz), postmortem examination showed that the baby was normally formed but had died of a massive aspiration of meconium

After a further two years she was admitted at term for a surgical induction of labour under general anæsthesia As she was not in labour in forty-eight hours after rupture of the membranes, a lower-segment cæsarean section was performed by J S T, delivering a boy weighing 9 lb 1$^1/_2$ oz (4125 g) in good condition

When first seen in her fourth pregnancy she was a fit woman, aged 36 years, height 5 ft. 5 in She had slight varicose veins of the right leg and a recent rash on her fingers which she attributed to a wasp sting At every antenatal attendance the height of the uterine fundus was noted to be greater than the duration of the pregnancy warranted. When Mr J D S Flew examined her at eighteen to twenty weeks the uterus was the size of a thirty-week gestation Radiographic studies revealed triplets (fig 1) and are reported in detail below At the thirty-first week the abdominal girth was 46 in, and at the thirty-third 48 in Symptoms of pre-eclamptic toxæmia were present for the first time at thirty-five weeks the blood-pressure was 145/90 mm. Hg and there was a trace of albumin in the urine and slight peripheral œdema, so that the patient was kept on strict bed rest. The next day these abnormal signs had disappeared

During the morning of delivery there was a small but definite show of blood per vaginam The membranes were intact. The patient was well, three fœtal hearts were heard, and there were no uterine contractions It was decided to deliver by cæsarean section that day because of the previous history and the known presence of fœtal abnormality in a multiple pregnancy Under general anæsthesia (thiopentone, suxamethonium, gallamine, and cyclopropane) a classical section was performed. The first baby was delivered by the breech at 6 45 P M, he cried at once and was in excellent condition The second amniotic sac was opened and twin boys joined at the cranial vault were delivered simultaneously at

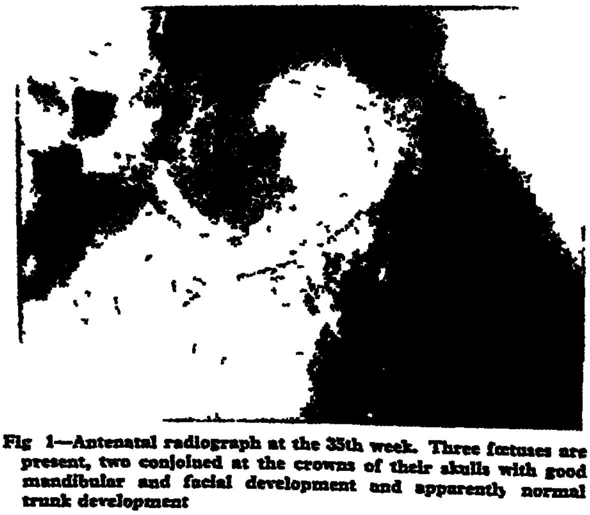


Fig 1—Antenatal radiograph at the 35th week. Three fœtuses are present, two conjoined at the crowns of their skulls with good mandibular and facial development and apparently normal trunk development

6 48 P M Both cried at once None of the babies presented any resuscitation problem, but in all mucus was cleared from the air passages Ergometrine 0 5 mg was injected intravenously into the mother and the same dose directly into the uterine muscle after the delivery of the babies The previous lower segment operation scar was palpated and estimated to be 3 mm thick The uterine cervix was dilated to the diameter of two fingers' breadth Postoperative progress was uneventful except for pyrexia of 100°F on the first and third days

The placenta (fig 2) was an intimately fused organ with two amniotic sacs which did not communicate

Antenatal Radiographic Studies

The first abdominal radiographic studies at the nineteenth week showed three fœtal spines, indicating the probability of triplets That only two skulls were seen, indicated some fœtal anomaly, possibly anencephalus At the 28th week the radiographs were interpreted as showing one normal fœtus and a twin with two separate trunks and a gross cranial fusion At the 35th week immediately before delivery by cæsarean section craniopagus twins were clearly seen with two normal trunks and good mandibular and facial development The third fœtus showed no abnormality (fig 1)

The Triplets

The first baby (a male weighing 5 lb $9^{3}/_{4}$ oz , 20 in long, skull circumference $13^{1}/_{2}$ in) has appeared completely normal throughout He was successfully breastfed and at twelve weeks weighed 13 lb 12 oz

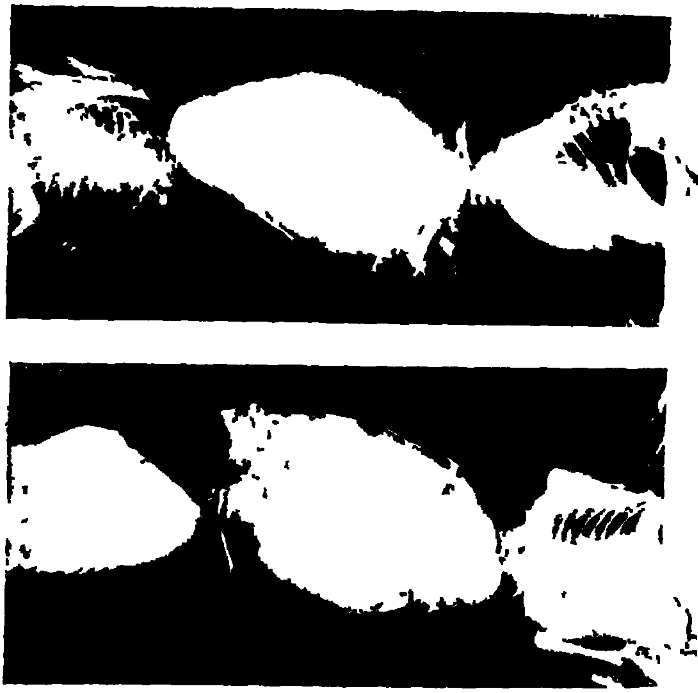
The craniopagus twins, also males, together weighed 9 lb 12 oz The vertices have virtually coalesced so that one skull cannot be moved on the other They lie in a straight line, their long axes twisted through somewhat more than a right angle This allows both to lie on the right or on the back while the face is turned half right When on the left side the neck is strained and they are not comfortable

General examination reveals no other abnormality Rectal temperature readings differ and so do pulse and respiration rates, which do not synchronise Simultaneous blood-pressure readings show 60 mm Hg systolic in one and 50 mm in the other Both are blood-group O, rhesus positive figures for Hb, white-cell count, and differential leucocyte count are not identical Electrocardiograms differ in rate and pattern, both having a physiological degree of right preponderance Electroencephalograms soon after birth, kindly carried out by Dr G Pampiglione, showed the brains to be separate

Fig 2—The placenta

The twins are two distinct individuals with independent behaviour and personality One may cry or feed while the other sleeps One is bigger and stronger, but both are full of charm and mentally alert, and they do not appear to upset each other

Clinical progress of the smaller twin has been interrupted by severe vomiting from eight to twelve weeks Projectile vomit of curds with visible gastric peristalsis, and a palpable pyloric tumour, supported the diagnosis of congenital hypertrophic pyloric stenosis Symptoms were relieved by a course of atropine methonitrate ('Pylostropin')



Figs 3 and 4—Radiographs shortly after delivery, taken in two planes at right-angles There is craniopagus with parietal fusion over a wide area The long cranial axes of the two heads are approximately at right angles to one another Facial bone formation of both appears perfect

In radiographs of the conjoined skulls (figs 3 and 4) no bony shelf can be seen between the vertices Parietal fusion exists over a wide area The long cranial axes of the two heads are approximately at right angles to each other Facial bone formation of both appears perfect

Discussion

Questions of ætiology are well discussed in some of the papers we have quoted, especially by Robertson (1953) We can only add that the presence of pyloric stenosis in one of the twins exemplifies the principle pointed out by Aird (1954) that conjoined twins " are seldom so precisely identical as separate monovular twins are " The future action in this case could not be better planned than in accordance with Aird's further statement that " however great the risk of the death of one or both children, it would seem that operation should nearly always be undertaken if the children are known each to have a full complement of the organs and tissues necessary for separate life "

In Cameron's case emergency operation failed, in Barbosa's (1949) both died three hours after operation, in Robertson's (1953) operation had to be abandoned The three latest reports of partial or complete surgical success are quoted above In this case great difficulty is likely to be encountered and the final separation will not be attempted before the first birthday To achieve separation with the survival of both twins will require not only great prowess on the part of the surgeons but also sufficient tissues for two independent beings To achieve one survivor will amply repay the great demands on the skill, the patience, and the emotions of all concerned Fortunately it was possible to avoid publicity in this case for more than three months, giving the parents some time to recover from the immediate emotional shock

Attempts to satisfy public curiosity about previous conjoined twins put a strain on parents, doctors, and nurses. It is hoped that in this case newspapers and their representatives will exercise restraint and allow all those involved to conduct a hazardous undertaking in calm and peace. The authors (and the parents, with whom it has been discussed) feel that no photograph of the conjoined twins should under any circumstances be published during the lifetime of either twin.

REFERENCES

Aird, I. (1954) *Brit med J* i, 831
Baldwin, M., Dekaban, A. (1958) *J Neurol Psychiat* 21, 195
Barbosa, A. (1949) *Rev bras Cir* 18, 1047
Cameron, H. C. (1928) *Lancet*, i, 284
Grossman, H. J., Sugar, O., Greeley, P. W., Sadove, M. S. (1953) *J Amer med Ass* 153, 201
Münster, S. (1559) Cosmographiae Universalis, Lib 3, 625
Robertson, E. G. (1953) *Arch Neurol Psychiat* 70, 189
Voris, H. C., Slaughter, W. B., Christian, J. R., Cayia, E. R. (1957) *J Neurosurg* 14, 548

POST-HOSPITAL ADJUSTMENT OF CHRONIC MENTAL PATIENTS

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UNTIL recently, once a patient had stayed for two years continuously in a mental hospital, his chances of discharge were low (Kramer et al. 1955, Carstairs et al. 1955) and would become progressively lower until, by the eleventh year of stay, they would be about 1 in 100 (Registrar General 1955). This situation may now be changing.

The Royal Commission on the Law Relating to Mental Illness (1957) stated a new viewpoint:

> "There is increasing medical emphasis on forms of treatment which can be given without bringing patients into hospital as in-patients or which make it possible to discharge them from hospital sooner than was usual in the past. It is not now generally considered in the best interests of patients who are fit to live in the general community that they should be in large or remote institutions such as the present mental or mental deficiency hospitals . . . No patient should be retained as a hospital in-patient when he has reached the stage at which he could return home if he had a reasonably good home to go to."

Brill and Patton (1957) and Kramer and Pollack (1958) show that in the United States in 1955–56, the year in which the use of tranquillising drugs became widespread in that country, the number of patients resident in State Mental hospitals declined, in reversal of a long-established trend. Brill and Patton showed that in New York State this could largely be ascribed to an increase in the number of discharges, especially affecting patients who had been more than two years in hospital. Neither Brill and Patton nor Kramer and Pollack (1958) indicated the level at which patients were functioning after their discharge from hospital.

Usually a psychotic patient discharged after a prolonged stay in hospital is not completely recovered but carries at least some residual disability. His remaining in the community will depend partly on the nature and degree of this psychiatric handicap and partly on the social environment to which he returns.

There have been many follow-up studies of former mental patients in general, and of patients with particular diagnoses or who have been exposed to particular forms of treatment (in most of which a stay in hospital of more than two years is claimed to carry a relatively unfavourable prognosis), but we have been able to trace only two studies which dealt specifically with the fate of long-stay patients after discharge from hospital.

Smith (1946) reports the outcome of 56 females who had been in hospital at least four years before discharge from St. Hans Hospital, Denmark. 54 of these still had symptoms, most required considerable help from social agencies. During the follow-up period (ranging from nine months to three years) 6 of these patients were readmitted and 1 committed suicide. Of the 49 who remained in the community only 6 were self-supporting.

Stringham (1952) reported the outcome of 33 patients discharged after an average stay in hospital of twelve years. 15 returned to hospital, but 6 of these were subsequently discharged again. Of the 24 still in the community about two years later only half were self-supporting. Stringham suggested that opposition on the part of the patient's family was the principal obstacle to their remaining in the community, and their ability to obtain gainful employment was the strongest positive factor in those who succeeded.

The present study was designed to ascertain the outcome of long-stay patients discharged from mental hospital and to look for factors in their history and in their subsequent social experiences which were associated with their level of adjustment in the community.

Method of Investigation

Selection of Cases

The population consisted of all those male patients who were discharged by any means from seven mental hospitals in or near London between July, 1949, and June, 1956, and who fulfilled the following criteria:

(1) Subjects of the United Kingdom by birth.
(2) Aged 20–65 on discharge.
(3) Had been in hospital two years or more before discharge.
(4) Not known to have gone to an address outside the Greater London Area.

Patients who died in the first year of discharge were excluded from the sample. There were 3 such deaths during the period, all of them natural. Patients who were out on trial for more than three months consecutively were included as from the end of the three-month period.

Selection of Informants

Whenever possible the primary informant was the housekeeper of the domestic group to which the patient went on leaving hospital—typically his mother, wife, or sibling, but in some cases his landlady. Any patient living alone was himself interviewed.

Follow-up Interview

An interview schedule was prepared covering 160 items, selected on the assumption that they might have a bearing on the patient's outcome. The schedule was usually completed for each patient after a study of the hospital case-notes and an interview with the primary informant lasting an hour to an hour and a half. Sometimes more than one person was interviewed.

The conduct of the interview was not formalised, but interviewers used a check-list to ensure that all the items had been covered. Each of us took part in interviewing, with weekly meetings for discussion of possible ambiguities in the recording of particular items, in this way it was hoped to ensure uniformity in the recording of data from the interview.

Measures of Outcome

For the purpose of analysis each patient's outcome was assessed in terms of the following criteria

(1) *Duration of discharge period* —" Success " (s) was defined arbitrarily as staying out of hospital for at least a year, readmission for more than a month in the year following discharge was counted as " failure " (F) This criterion of success proved to be relevant, especially for schizophrenia Since information was obtained at intervals of one to six years after discharge, it was possible to calculate that, of the patients who relapsed during the six years, 74% of the schizophrenics and 58% of the non-schizophrenics did so within the first year

(2) *Level of social adjustment* —All patients counted as successes were rated by a scale of social adjustment, in which 1 point was given for each of the following three items (*a*) being gainfully employed for five of the last six months in the first year of discharge, (*b*) being able to look after himself as regards appearance, dress, and use of money, and (*c*) showing adequate interpersonal relationships—i e, without gross disturbances such as violence, paranoid ideas, or extreme withdrawal

A score of 3 points rated " full adjustment ", 2 points " partial adjustment ", and 1 or 0 points " poor adjustment "

Some Characteristics of Population Studied

From the records of the seven hospitals 240 men were identified who fulfilled the necessary criteria, and schedules were completed for 229 (95%) Follow-up information could not be obtained for 11 of the original population, of whom 9 were diagnosed as schizophrenic, 1 as depressive, and 1 as psychopathic A search of the records of the Board of Control did not reveal evidence that any of these 11 patients had been readmitted to mental hospitals since discharge, all have been omitted from our analysis

Diagnoses

The diagnoses of the population studied were as follows

	No of cases
Schizophrenia	156
Depression	26
Epilepsy	18
Organic psychoses	10
Psychoneuroses	9
Mania	5
Other	5
Total	229

If the population is then divided into two main categories " schizophrenia " and " other " it can be further described in terms of the following factors

Age —The mean age of schizophrenics was 39 4 and of those with other diagnoses 45 0, in both the age range was 20–65

Length of stay —The two main categories of diagnosis had comparable lengths of stay for the admission to hospital which preceded this discharge, with a mean of 6 5 years (range 2–30 years)

First admissions —31 4% of schizophrenics and 43 8% of those with other diagnoses were first admissions

Marital status on admission —77 6% of the schizophrenics and 42 5% of the others were single on admission

Patients' Condition on Discharge

Before assessing the patients' outcome one would like to know as accurately as possible their mental state at the time of discharge, but in this retrospective study precise information on this point was unavailable Some measure of the patients' mental state was, however, provided by the following observations

(1) *Whether discharged on or against medical advice* —31% of schizophrenics and 15% of the others were discharged against advice

(2) *Whether recorded as recovered, relieved, or not improved on discharge* —Of the schizophrenics 14% were discharged as recovered, 65% as relieved, and 21% as not improved, for the other patients the proportions were 13% recovered, 7 relieved, and 10% not improved

(3) *A rating of the patients' level of disturbance of behaviour* while living in the community a year after discharge or just before readmission in the case of failures —This was estimated on the basis of questions about ten specific features of the patient's behaviour and was rated in three categories Patients who showed only minor peculiarities, or none, were rated " nearly normal " Patients with evident peculiarities which did not, however, preclude their moving about in society were rated " moderately disturbed " (e g, a patient with hallucinations and paranoid ideas who found a succession of jobs to quit them abruptly in response to his delusions) Pati showing more severe disturbances of behaviour, such as to be cited in recommending certification and interfered seriously with his social life, were rated " severely disturbed " It w be appreciated that this rating made at a later date can only giv a somewhat conjectural (but still useful) indication of patient's condition on discharge

Of the schizophrenic patients 39% were rated near normal, 35% moderately disturbed, and 26% severe disturbed, of the remainder 45% were rated nea normal, 36% moderately disturbed, and 19% severe disturbed

Findings

Measures of Outcome

32% of the total population were failures and 68 successes, percentages were comparable for schizophre and other diagnoses

Table I shows that other diagnoses have a sligh superior but non-significant (p>0 1) distribution social-adjustment scores 26% of the total populatior showed a very satisfactory or full social adjustmen (93% of these were rated nearly normal in behaviour), whereas 22 8% made a definitely poor adjustment, 18 9% were intermediate between these two social adjustment categories

TABLE I—SUCCESSES AND FAILURES

Diagnosis	No of cases	Successes (%) by level of social adjustment			Failures (relapse in 1st year) (%)
		Full (3 points)	Partial (2 points)	Poor (1 and 0 points)	
Schizophrenia	156	25 2	17 4	25 8	31 6
Other	73	28 8	21 9	16 4	32 9
Total	229	26 3	18 9	22 8	32 0

Table II shows the distribution of the three-fo behavioural ratings by schizophrenia and other diagnose and by success or failure 40 8% of the total populatio were rated nearly normal, 35 2% moderately disturbe and 24 2% severely disturbed The ratings are related success or failure

Relation of Outcome to Clinical State on Discharge

The two indicators obtained from patients' ca notes (" discharged against advice ", and " recovered " relieved ", or " not improved " on discharge) were br related to our criteria of outcome (With the crite of success or failure both showed a coefficient of co

TABLE II—BEHAVIOUR

Diagnosis	No of cases	Nearly normal (%)		Moderately disturbed (%)		Severely disturbed (%)	
		Success	Failure	Success	Failure	Success	Failure
Schizophrenia	156	37 8	1 3	23 1	11 5	7 7	18 6
Other	73	38 9	5 6	20 8	15 3	6 9	12 5
Total	229	38 2	2 6	22 4	12 8	7 5	16 7

gency* of 0 24, p<0 001, with the three-fold social-ustment rating the coefficients were 0 32 and 0 26 pectively, p<0 01)

The rating of patients' level of behaviour was also related with outcome, both in terms of success or lure, where C was 0 50 for the schizophrenics and 0 38 the others (p<0 001), and of social adjustment, which s rated in part on observations of patients' behaviour It is therefore clear that, in assessing subsequent ationships between clinical and social factors and the tients' outcome, a first precaution must be to ensure at the relationship is not a reflection of the patients' fering levels of clinical state at discharge In many of e following instances the above indices of clinical state discharge have been used to counteract crude clinical bias

e-discharge Items

Number of previous admissions—The relationship of is item to outcome differs for the two diagnostic cate-ries, schizophrenia and other diagnoses 31% of the hizophrenics were first admissions, and only a few 7%) had been in hospital three or more times before his small category contained relatively more failures 2 successes and 15 failures, p<0 01) but showed no lationship with social-adjustment scores In contrast, her diagnoses had a greater number of first admissions 4%), of whom only 3 of 32 failed In this diagnostic oup the number of failures increased significantly in the roup of patients who had been in hospital before, compared with the first admissions (21 of 41 failed, p<0 001) gain no relationship was found with social-adjustment cores

Length of key admission—For neither schizophrenia or other diagnoses did the length of key admission bear ny direct relationship to success or failure, nor for other diagnoses did it relate to social-adjustment scores However, for schizophrenia those with poor adjustment were mainly concentrated in those with less than ten s' stay (p<0 05), although trends are not striking, chizophrenics with longer stay in hospital had a slightly superior outcome

Age at discharge—Only 2 of the 17 schizophrenics aged more than 55 failed Otherwise age bore no relationship to success or failure either for schizophrenia or for other diagnoses As regards social adjustment, however, the younger schizophrenics, aged 20–34, were significantly more often poorly adjusted (p<0 01), whereas other diagnoses showed no such relationship

Pre-admission levels of social achievement—Various measures of pre-admission achievement were obtained in e areas of employment and economic responsibility uperior achievement was usually significantly related to ost-hospital success and to higher social-adjustment cores The relationships still remained when clinical tate at discharge was taken into account

Post-discharge Experiences and Outcome

The two most important factors in the social experience a discharged patient were whether the patient worked not and with whom he lived

Employment—Table III shows an important relationship between employment and success or failure 41% of the population worked for six months or more, and of these 97% succeeded, whereas of the 43% who were never employed only 46% succeeded Of the 89 successful patients who worked for most of the year a third were rated as either moderately or severely disturbed, and many of the others had residual symptoms, indicating that the presence of psychotic symptoms was not necessarily a serious obstacle to their employment

TABLE III—EMPLOYMENT

Employment	Successes	Failures	Total
6–12 months	89	3	92
1–6 months	19	18	37
Unemployed (includes those working less than a month)	44	52	96
Information inadequate for rating	4		4
Total	156	73	229

Type of living group—The results so far presented take on new significance when tabulated by type of living group to which the patient returned The significance of the social setting on discharge has been more fully analysed by one of us (G W Brown, unpublished), only the chief points are noted here

Table IV shows that schizophrenics who returned either to parents, wives, or hostels relapsed in the first year significantly more often than did those returning to other kin (mainly siblings) and lodgings Those who did succeed while living with their parents had significantly lower social-adjustment scores than patients living with other kin or in lodgings Fewer living with parents were employed compared with the successful patients living with their wives, with other kin, or in lodgings

Relatively more patients rated not improved on discharge went to stay with their parents or in hostels, but these differential failure rates and social-adjustment scores still persisted at a significant level when this bias was controlled This indicates that the type of living group to which a patient goes after leaving hospital may have an important bearing on his subsequent career, whatever his residual disabilities are

Psychiatrists are familiar with the mother who tolerates, and perhaps even encourages, an attitude of child-like dependence in her schizophrenic son This kind of relationship was especially common in the 53% of unemployed schizophrenics living with their parents and was very rarely found in other types of living group Perhaps it is not always beneficial for a schizophrenic to return to the close emotional ties of a parental or marital household

There was some evidence that behaviour deteriorated more in schizophrenic patients who went to parental and marital groups For example, the relative incidence of violent outbursts and displays of temper was significantly greater in these groups, whereas other psychotic manifestations (e g, delusions) were more often reported for patients living with other kin and in lodgings

Where a schizophrenic lived with his parents and was unemployed, with the result that he was brought into close contact with his mother all day, he was likely to fail, but if he or his mother were away at work for part of each day, he was more likely to succeed

TABLE IV—WHERE LIVING

Where living	Schizophrenia			Other diagnoses		
	Successes	Failures	Total	Successes	Failures	Total
Hostel	6	7	13	4	7	11
Hostel (supportive)	1		1	4	3	7
Parental	55	31	86	8	8	16
Marital	7	7	14	16	1	17
Other kin (mainly siblings)	20	4	24	9	3	12
Lodgings	18		18	8	2	10
Total	107	49	156	49	24	73

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* Uncorrected coefficients of contingency derived from χ^2 results are used. The maximum for a 2 × 2 relationship is 0 707 and 3 × 3 is 0 816

TABLE V—MARITAL STATE

Marital state	Schizophrenia		Other diagnoses	
	Successes	Failures	Successes	Failures
Married	7	7	16	1
Widowed, separated, or divorced	16	2	11	14
Total	23	9	27	15

The relationship of outcome and post-hospital living group was less clearcut in the patients with other diagnoses, but there was some evidence that they, unlike the schizophrenics, tended to do better in situations involving close personal relationships. For example, table V shows completely contrary results for patients of the two diagnostic groups in respect of their marital state at discharge.

Of the 16 patients with other diagnoses who succeeded in a marital setting 7 were unemployed. In contrast, of the 7 schizophrenics who succeeded in a similar environment 6 were employed. These figures suggest that wives found it easier to tolerate a state of dependence in patients of the former group. A factor which *may* have contributed to this greater tolerance was the presence of a physical ætiology or physical handicap in 6 out of the 7 unemployed men in this group. These patients were easier to live with and responded more positively to the support offered to them than did the schizophrenic husbands, whose behaviour in several instances was much disturbed.

Aftercare

Only 37 of the 229 patients (16.2%) were reported to have attended an outpatient clinic for follow-up treatment. One or more visits were paid by a psychiatric social worker to 39 patients (17.0%). In neither of these small groups did the outcome differ significantly from that of the remainder.

Social Liabilities Incurred

To reach a just estimate of the outcome of these patients it was necessary to take into account not only their success in avoiding relapse and in attaining a fair level of social adjustment but also the consequences to other persons of the patients' return to living in the community. In some instances the patient's success was bought at the price of occasioning severe distress to others in his household.

A three-fold rating was therefore made of the amount of hardship which the patient's presence imposed on other members of his living group. The rating "severe liability" was reserved for those cases in which the patient's deranged behaviour caused considerable hardship to others—e.g., through violence (which was displayed by 63% of patients in this category), sexual deviation, callousness, paranoid accusations, and threats of suicide.

Where the patient's behaviour caused less serious hardship, the rating "moderate liability" was given, and patients whose symptoms, if noticeable at all, caused no obvious distress to others were rated "minimal liability". This estimate was influenced by the attitude of the other members of the household, some of whom found even slight psychotic symptoms very disconcerting, whereas others (especially certain mothers) showed extreme indulgence.

17% of the total sample were rated severe liability, 28% moderate liability, and 55% minimal or no liability. Many of the patients who caused distress to others (79% of those rated severe and 44% of those rated moderate liability) relapsed within the year.

The category severe liability included 16 patients who were discharged against medical advice, either after an escape *or at their relations'* behest, but proved too difficult to cope with in the home, as in the following example.

Case 1.—Discharged after his third admission for schizophrenia, which he had had for eleven years. Still profoundly disturbed, liable to attack his mother and step-father in sudden outbursts. These attacks were tolerated, but when he began to make sexual demands on his sister he was returned to hospital.

Among the 156 successes there were 36 patients (23%) who caused moderate hardship to others and 8 whose presence in the household caused severe hardship. In the latter group it was evident that the burden of a very disturbed patient had only been transferred from the hospital to the home. 4 of these patients lived with their parents, *3* with their wives, and 1 with a foster-sister.

At the other extreme, patients rated as minimal liability *tended to have a favourable outcome*, except for *24* men who went to live in Rowton Houses, Salvation Army hostels, or other institutions. 11 of these returned to hospital, for the most part of their own choice. These probably form part of the group of long-stay patients referred to in the Royal Commission report as "having reached the stage at which they could return home if they had a *reasonably good home* to go to."

It is in the intermediate category of patients presenting moderate liability that attitudes of persons in their immediate environment might especially be expected to influence the outcome. A typical example was the following.

Case 2.—Schizophrenic, aged 26, taken home against advice. Remained at home nearly two years although not well enough to work, often hallucinated, afraid to be left alone, and conspicuously strange in manner. "You could not take him out to meet people." Parents lived in a genteel suburb and were embarrassed by son's appearance, their social activities were much restricted while he was at home.

Discussion

Previous follow-up studies have emphasised the diminishing chances of recovery of patients whose stay in mental hospital is prolonged. Smith (1946) and Stringham (1952) reported a poor outcome for the discharged chronic psychotic. In contrast, the present study showed that 2 of 3 long-stay patients succeeded in remaining in the community for at least a year after discharge, and that 2 of 3 of these successes were maintaining a viable social adjustment. In contrast to the usual findings with early cases, the outcome bore little relation to the patients' ages, recorded diagnoses, or length of stay in hospital, it did, however, bear a significant relationship to the social group to which they returned and to their employment record.

It is no new discovery that it is sometimes inadvisable for schizophrenic patients to return to their own families, the point has been made in many of the standard textbooks of psychiatry, and it provides one of the arguments in favour of foster-homes. The present study, however, makes it possible to support the assertion with a substantial series of instances. Freeman and Simmons (1958), discussing the outcome of male psychotics discharged after a short stay in hospital, contrast the outcome of those who returned to conjugal and to parental settings and conclude that wives have higher expectations of performance in relation to the recovered patient than do parents. Patients are just as likely to fail in the conjugal setting, but if they survive they do so at a higher level of social functioning

The importance of employment as a preventive of relapse is emphasised by Cohen (1955), who showed that, when chronic schizophrenics left a Veterans' Hospital, their success in avoiding relapse was not related to the continuance of minor symptoms but was significantly related to their success in finding work, and that this, in turn, was related to the amount of vocational planning before the patients left hospital The present study suggests that employment is not only beneficial for the patient but also makes it easier for the household to tolerate a mentally handicapped member In this connection it may be noted that many of the patients who were unemployed were judged by the investigators to be capable of working. If they could have been offered sheltered employment pending their return to normal work, their chances of survival in the community would have increased

To help in finding jobs and suitable accommodation is a principal function of the psychiatric social worker It is no adverse criticism of them but rather a reflection of the volume of work which they have to undertake, that so few of these patients were able to profit from their services Nor were the patients the only ones who needed social-work help The assessment of "distress caused to others" revealed that in many cases the patient's household needed help in dealing with problems presented by his return "Community care" will not represent an advance in treatment if it means that a burden has merely been transferred from the hospital to the family As was shown some years ago for shock treatment (Feldman et al. 1947), it may be necessary to intensify the provision for aftercare so as to derive the full benefit of the new emphasis on extra-hospital treatment of the mentally disabled

Summary

A follow-up inquiry was completed with 229 of 240 patients discharged after more than two years' stay in a mental hospital

68% of these patients succeeded in remaining out of hospital for at least a year, and 66% of these were rated as showing either full or partial social adjustment

Successful outcome was associated with patients' clinical state on discharge, with their subsequent employment, and with the social group to which they went Patients staying with siblings or in lodgings did better than those staying with parents, with wives, or in large hostels

In this group of patients the outcome bore little relation to patients' age, recorded diagnosis, or length of stay in hospital

The social liability presented by these patients to their households was estimated.

The need for supportive social work with ex-patients and their families is pointed out

REFERENCES

Bell, H, Patton R. E. (1957) *Amer J Psychiat* 114, 509-16
Carstairs, G M, Tonge, W L, O'Connor, N, Barber, L E D (1955) *Brit J prev soc Med* 9 187
Cohen L (1955) *Personnel and Guidance J* 34 28-32
Feldman, F, Susselman S, Barrera S E (1947) *Amer J Psychiat* 104, 402
Freeman H. E. Simmons O G (1958) *Amer sociol Rev* 23 147
Kramer M Goldstein H Israel, R H Johnson N A 1955 A historical study of the disposition of first admissions to a State mental hospital Public Health Monographs no 32 Washington D C.
— Pollack, E S (1958) (in the press)
Registrar General (1955) Statistical Review of England and Wales for the two years 1950-51 Supplement on General Morbidity, Cancer and Mental Health H.M.S.O 1955
Royal Commission on Laws governing Mental Illness and Mental Deficiency 1957 Report London
Smith J C (1946) [illegible] 21 735
Stringham J A (1952) *Amer J Psychiat* 108, 924

PSYCHIATRIC RESEARCH IN THE STATE OF ILLINOIS

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In the past ten years an astonishing change has transformed the field of psychiatric research At one time this field was almost equally barren of ideas, workers, and money A few small groups kept up a brisk pioneering enterprise, but the massive support available to other fields of medical research was lacking This has now quite changed, and the ideas, the workers, and the money are accumulating at an ever-increasing rate The ideas are those fruitful hypotheses of the chemical basis of schizophrenia that are leading to so much biochemical, pharmacological, and physiological work on the ætiology of the psychoses[1] The new biochemical insights gained and the new drug therapies such as the group of phenothiazines have revolutionised psychiatry, as Dr Percival Bailey has recently proclaimed But the present article will be concerned with another aspect of this progress—the very essential one of the financial and administrative machinery that has made all this possible The increase in momentum of psychiatric research has been more noticeable in the United States than in England, and nowhere has this been so more than in the Department of Public Welfare, a branch of the State Government of the State of Illinois Psychiatric research in the United States is supported from four main sources—the great private Foundations, the Federal Government, the Armed Services, and the individual State Governments Each of these make contributions to the total, but this article will be concerned with just one part of one of these with which I am familiar

In 1949 the Legislature of the State of Illinois decided that the only way to combat the ever-rising costs of care of the mentally ill was to organise research in psychiatry A plan was devised whereby money paid to the State by the patients and the relatives of patients in the State psychiatric hospitals should be devoted to psychiatric research and training This money contributes towards a special Mental Health Fund which is devoted to six main projects (1) psychiatric research, (2) training of medical, nursing, and other professional staff, (3) mental health education of the general public, (4) community mental health services, (5) service improvement projects (i e, studies of the system designed to improve its efficiency), and (6) administrative costs of the other five projects (e g, the cost of collecting the money from relatives)

The fund runs on a biennial budget, and this for the years 1957–58 amounted to $24,000,000, of which some $7,000,000 came from the payment made by the patients and their families The portion of this devoted to psychiatric research and training during this two-year period was some $4,000,000, of which about half was devoted to research This fund is administered by a special body—The Psychiatric Training and Research Authority set up within the Department of Public Welfare with the advice of the Illinois Psychiatric Advisory Council to which members are appointed by the Governor and which meets once a month. It consists of the heads of the Department of Psychiatry of the Chicago medical schools, of the Michael Reese Hospital (a leading centre for psychosomatic medicine), and of the Institute for Psychoanalysis as well as Dr Otto L Bettag, the director of the Department of Public Welfare

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[1] Smythies, J R. *Lancet*, Aug 9, 1958, p 308

The main centre of psychiatric research in Illinois is not set in Chicago as one might have expected but in Galesburg, a pleasant little town of some 30,000 inhabitants in Western Illinois The Galesburg State Research Hospital is one of the only five hospitals in North America that has been fully accredited by the American Psychiatric Association and is one of the most modern and up-to-date hospitals in existence It is built on the villa principle, and each villa holds 30–40 patients The research laboratory is directed by Dr Harold E Himwich, a ranking authority on the chemistry of the brain, and the work is devoted to studies of the biochemistry and pharmacology of the nervous system Important work has been done on the pharmacology of the reticular formation and of hallucinogenic and phenotropic drugs, on the biochemistry of maturation and ageing, on the chemistry of psychosis, the clinical evaluation of new drugs, and other related subjects

But I am dealing with administration rather than with the research itself, and it will interest British readers to learn that the research budget of the laboratory for funds devoted solely to salaries, equipment, and materials is $883,220 for the biennium, the significance of which I will return to below The State also supports at Elgin State Hospital a biochemical laboratory that operates on a budget of $148,000 with other sources of funds outside the State and two projects at Manteno State Hospital under Dr Nathaniel Aptner at a rate of $66,000 a year The Mental Health Fund also finances a large number of projects in the universities of the State The main one of these is the Illinois Neuropsychiatric Institute (a section of the University of Illinois) Here work is being carried out in neuropathology, on the tissue-culture of neurones, and on biochemical changes in schizophrenia Twelve other projects are being conducted in various branches of the University of Illinois bringing its yearly share to $350,000 The University of Chicago has two projects at $80,000, the Michael Reese one at $34,000, Chicago Medical School one at $23,000, and Loyola University one at $26,000 These projects cover child psychiatry fairly substantially as well as purely biological problems

In spite of this lavish outlay, income for the first few years of the projects has accumulated faster than it was spent, and these accumulated funds have been used to build two new psychiatric research hospitals in Chicago The Illinois State Psychiatric Institute is now complete at a cost of $9,000,000 and is truly a magnificent building It will be run by the Department of Public Welfare and staffed mainly by five services from the Chicago medical schools The second hospital will cost $5,500,000 and is a pædiatric hospital for mental defectives These two hospitals will undertake extensive research and training of psychiatrists

Now to devote some attention to the input side of the money flow—to use a cybernetic analogy The charges for inpatient care in the State hospitals are set by the Department of Public Welfare for each case after a careful consideration of the patient's financial resources and these charges vary from a maximum of $81 a month to nothing The patient or his family is free at any time to dispute these charges in the courts, although this is in fact very seldom done It should be remembered that here is no National Health Service of any kind in the United States, and so people expect to pay for the servi that they receive in hospitals

In conclusion it is interesting to note that the resear budget of the Galesburg State Research Hospital (sp wholly on salaries for research workers, goods, an equipment) is $441,600 a year The total expenditu from Government sources in the U K for the year 195 on psychiatric research came to £83,000[2] which i equivalent to $410,000 (counting £1=$5, the cost-o living equivalent)

The enlightened mental health research programme the State of Illinois is financed by those personally mo interested in the discovery of the cause and cure of ment illness—the patients themselves and their families— whereas the total cost of maintaining the patients is born by the State This bold scheme is already spreading in th States and has been adopted by Louisiana As it is much smaller and poorer State than Illinois its researc and training budget is only $350,000—which is never theless a respectable sum

I am most grateful to Dr Otto L Bettag, director of the Depart ment of Public Welfare, and to Dr Lester H Rudy, superintendent of the Galesburg State Research Hospital, for making available the facilities that have made this report possible

Medicine and the Law

Tale of Two Patients

A CORONER'S jury has returned a verdict of death by misadventure in a case in which the wrong patient was discharged from hospital[3]

A Mr Grange, who had been involved in a road accident, and who apparently had some deformity, was admitted to hospital at about 11 P M after being knocked down by a motor-car He was found by the casualty officer to be "moderately shocked" and was put to bed under observation An elderly man, also a road-accident case, was admitted the same evening, after treatment, his discharge was arranged provided that his own doctor was known so that a letter could be sent to him

The casualty officer went to bed, and was awakened at about 2 A M by his staff nurse She and another staff nurse apparently inquired if the crippled man could go home When the casualty officer did not answer, one of them added "the person under observation" The casualty officer then said that the man could go if he had a letter for his doctor

The casualty officer was awakened again at 6 A M and was told that a doctor had telephoned to say that he was returning a patient because he thought he was suffering from internal hæmorrhage It was then that the casualty officer discovered that Mr Grange and not the elderly man had been allowed to leave Mr Grange died a few hours later

At the inquest a consultant surgeon said that, ideally, the patient's record card should have been taken to the doctor "That is being wise after the event"

The coroner told the jury "It might seem to you that things have been rather lackadaisical but there is no evidence of negligence of a kind which is likely to lead to a charge of manslaughter" It would be wrong for them to word their verdict in a way that might show that they were trying to decide some question that could be settled in a civil court

The coroner also told the jury that he did not think it necessary for them to add anything to their verdict, as senior officials of the hospital were present "I feel that we can rely on the hospital, if there is need for tightening up to be done"

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[2] *Hansard*, Jan 27, 1958, col 24 This figure is taken from a written report by the Minister of Health It includes £58,000 from Exchequer funds spent by the Medical Research Council and £25,000 spent within the National Health Service It does not include expenditure on research in universities and medical schools

[3] *Newcastle Journal*, Sept 12, 1958

Public Health

BRONCHITIS AND THE ACIDITY OF URBAN PRECIPITATION

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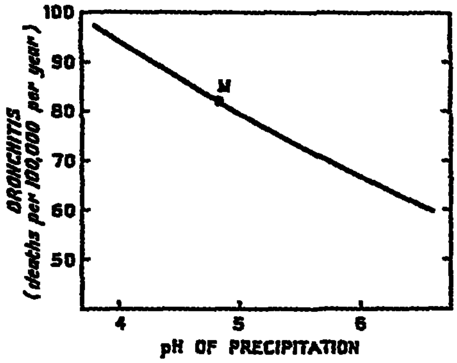
THE incidence of bronchitis is uncommonly high in Britain, especially in urban areas during winter, and it has been conjectured that air pollution is at least partly responsible. In this paper I report a correlation between bronchitis mortality and the acidity of urban precipitation

The mortality-rates for bronchitis were calculated from the Registrar General's annual statistical reviews for the whole populations of fifty-three county and Metropolitan boroughs in England, Scotland, and Wales over the five-year period 1950-54, and plotted on scatter diagrams versus air-pollution data from single stations and periods within these boroughs These latter data were extracted from table 8 of the 27th Report of the Department of Scientific and Industrial Research on the investigation of atmospheric pollution (1955), which provides figures for the monthly atmospheric deposit of tar, ash, other combustible matter and sulphate per unit area in urban districts, and also gives the pH of the precipitation Of all these, only the last two showed any obvious relationship with the bronchitis death-rates, and a more detailed statistical treatment was then carried out, using in this case averages of all the pH and sulphate values given for the winter months September to March in each of the fifty-three boroughs To obtain a more normal frequency distribution, and also a more linear regression, a logarithmic transformation of the bronchitis death-rates and of the sulphate deposits was employed.

The logarithmic correlation coefficient (r) for bronchitis and winter pH of precipitation amounted to −0·49 a value significant at the 1% level The corresponding coefficient for bronchitis mortality and winter sulphate deposit, which is no doubt related to the production of sulphur dioxide from fuel combustion, amounts to −0·32, a value significant only at the 5% level

To test further the above relationships, partial correlations of bronchitis mortality with the pH of winter precipitation and with the winter sulphate deposit were carried out, in order to eliminate the effects of any correlation between the two environmental variables Following this procedure, the coefficient of correlation (first-order) between bronchitis mortality and pH of winter precipitation fell only slightly to −0·45, a value still significant at the 1% level. In contrast, the correlation with sulphate deposit declined considerably, the first-order coefficient of −0·24 being no longer significant even at the 5% level. It is therefore unnecessary to consider this last correlation further

The partial regression equation relating bronchitis mortality (b, as deaths per 100,000 of population per year) to the acidity of winter precipitation (a, as pH) is $b = 192(0{\cdot}838)^a$ This relation is shown graphically in the chart, from which it may also be seen that the logarithmic average of the annual urban death-rate from bronchitis is 82 per 100,000 persons, or about 1·8 times the rural death-rate for the same period In those areas where rain pH is below 4, and hence strongly acid the death-rate reaches 100, while it is only about 60 in those urban areas with the least acid rainfall The rural death-rate for the same period is considerably lower even than this, at 46 annually per 100,000 of population, so acidity would not appear to be the only factor involved in the increased urban death rate, if in fact the acidity correlation is taken as truly causal While such an interpretation must of course be regarded with caution, it seems not unreasonable to infer that long-continued exposure to acid aerosols might increase the likelihood of bronchial inflammation In this connection it must be borne in mind that during dry weather the aerosol droplets will be considerably more acid than the ultimate raindrops in which they are precipitated, and may well exhibit pH values below 2 at times



The relation between bronchitis mortality and acidity of precipitation in urban areas. M gives the logarithmic mean death-rate.

Even in predominantly rural areas the rainfall may be quite strongly acid For instance, in the English Lake District rain pH averages less than 4·5, and goes below 4 on occasions, owing to atmospheric supply of sulphuric acid with easterly winds from the great industrial areas (Gorham 1958a) Surprisingly, however, in the industrial cities themselves hydrochloric acid seems likely to be the chief cause of low pH values (Gorham 1958b) The effects of both these strong mineral acids on bronchial tissues might well repay detailed investigation

I am much indebted to Mr David Driver for help with the calculations.

REFERENCES

Department of Scientific and Industrial Research (1955) Report on the investigation of atmospheric pollution, no 27 H.M Stationery Office.
Gorham E. (1958a) *Phil Trans Roy Soc.* B, 241, 147
— (1958b) *Quart J R Met Soc.* 84, 274

Strontium 90 and Malignant Disease

A report in the *New York Times* of Sept 20 refers to new work on the important question of whether or not there is a threshold level of ^{90}Sr in bone, below which no bone cancer or leukæmia is induced The work is that of M P Finkel at the Argonne National Laboratory in Lemont, Illinois, and it is described in detail in *Science*, in an issue which has not yet reached us ^{90}Sr was injected in varying doses into 810 mice, and the incidence of tumours and length of life in this group was compared with those of an uninjected control series According to the *New York Times*, the results suggested that no damage was done by small doses—in other words, there *was* a threshold in mice. From observations in cats and dogs, however, Miss Finkel estimates that ^{90}Sr is probably "seven to fourteen times more harmful to man than to mice, because of his greater size and other factors" Her conclusion is that the threshold for man is so much higher than present fallout levels that fallout is extremely unlikely to induce "even one bone tumor or one case of leukemia"

On the assumptions that no threshold exists and that weapon tests stop this year, the recent United Nations report[1] estimated that fallout radiation may produce 400 to 2000 cases of leukæmia a year Assuming a threshold of 400 rem, the U N Committee's figure for fallout leukæmia dropped to zero

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[1] See *Lancet*, Aug 16, 1958, pp 355, 360

Congresses

TROPICAL MEDICINE AND MALARIA

The Sixth International Congress of Tropical Medicine and Malaria was held in Lisbon on Sept 5–13 under the presidency of Dr J Fraga de Azevedo (Portugal), with Sir Philip Manson-Bahr (U K) as an honorary president The palatial new building of the Portuguese Institute of Tropical Medicine, which has had fifty-six years of vicissitudes since its inception, was ready just in time for this occasion

Acclimatisation to Heat

Sid Robinson (U S A) summarised physiological adaptations to heat as (*a*) improvement in efficiency of evaporative cooling and in sensitivity and capacity of the sweating mechanism, (*b*) increase of circulating blood-volume during exposure, accompanied by improvement in circulatory stability, and (*c*) dramatic improvement in temperature regulation so that by the 8th day of exposure, men may perform work in heat with no greater elevation of rectal temperature or metabolism than when they perform the same work in a cool environment

D E Bass (U S A), however, reported a recent finding of venoconstriction and reduction of blood-flow in the forearm during work in heat, occurring only on the 3rd and 4th days of exposure, and suggested that such venoconstriction might improve cardiovascular performance by maintaining functional blood-volume, this led him to reconsider the concept that cardiovascular improvement resulted from actual increase in basal blood-volume

W V Macfarlane (Australia) discussed human water economy in the heat, aldosterone, and several interesting seasonal differences in body responses to fluid loss In winter, for example, plasma-volume did not fall on the loss of 3 litres of sweat, nor did antidiuretic substance (A D S) appear in the plasma, in summer, plasma concentrated with the same sweat loss and A D S appeared

C S Leithead (U K) reported a significant fall in hæmatocrit and circulating protein levels in men on their 4th day of exposure to heat in Kuwait, and interpreted this as evidence of increase in circulating blood-volume by hæmodilution Prior to this, tilt-board and exercise tests had revealed cardiovascular instability of the subjects, but giddiness and syncope appeared only in those who had never before been in the tropics and to whom, therefore, all was strange—climate, environment, and customs

This possibly cerebral effect was emphasised by E M Glaser (U K), who observed that acclimatisation to heat depended partly on stored information which modified some heat-regulating responses and which resembled habituation and learning Subjective responses to warming were also modified during acclimatisation to heat, and it seemed possible that this was also due to a cerebral mechanism of habituation

Heat Tolerance

R. K Macpherson (U K) described "heat tolerance" as a simple title for a complex subject When a man exposed to heat collapsed, the limit of physical tolerance had obviously been reached and passed, but long before that stage the man's powers of perception, reason, and judgment were impaired and it was difficult to say when such deterioration began Tolerance was also to some extent *affective* in that there would always be a limit to the willing endurance of discomfort

H S Belding (U S A) mentioned at least eleven indices or scales of heat stress, including the heat stress index (H S I) recently proposed by Professor Hatch and himself[1] Before accounting for such variables as sex, age, degree of acclimatisation, it was first necessary to index valid in application to young, fit, and fully men Even then, the factors affecting heat stress were f able enough temperature of air, solid surroundings and ambient skin and vapour pressures, air speed, bod area and postural attitude, body-heat production, cl time of exposure Each factor required quantitative and deficiencies of the present H S I lay in misestimates circulatory strain imposed upon the subject, his skin ture, and the effects of clothing

The problem of whether men working in spaces radiant-heat load is severe (e g , at furnace doors) be or seminude should be one of concern to industrial officers Professor Belding believed that clothing reduced heat stress by blocking radiation and convection conceded that it might reduce evaporation from the skin argued that increased sweat production which wetted clothing and thus gave a larger total surface for would be compensatory

F N Craig (U S A) from a study of the phys state of subjects at the end of their tolerance-times (i e, time period elapsing before voluntary withdrawal environmental heat stress) concluded that the total heat in the body was the critical factor in tolerance of heat As heat storage was calculable from metabolic rate, resistance of clothing, and environmental humidity, he suggested that this was a method of heat tolerance

F H Bonjer (Netherlands) described experiments men working at a brick furnace In such situations, wished to know the maximum allowable working-time and minimum required rest period after exposure As the mini heat gain of the body was calculable for a given set of stances, the maximum allowable working time could be puted by dividing the presupposed maximum allowable gain (i e , 1°C rise in body-temperature, or 60 KCal in a of average size) by the minimum heat gain per unit of Derivation of minimum required rest period after exposure more complex and required further investigation

A R Lind (U K) said that in emergencies such rescue operations in coalmines, men were sometimes requ to work in environments too severe to fall within the range existing indices of heat stress He had found, however, that simple weighting of wet (×0 85) and dry (×0 15) bulb temperatures related climates of similar severity, and this formul proved effective for wide variations of energy expenditure and clothing worn, although the range of air-movement investigated was limited

D M Kerslake (U K) said that heat-stress effects due to small increases in absolute humidity were large when the skin was completely wet with sweat, and recent experiments showed that they were much smaller when evaporation of sweat was complete Effects on skin and mouth temperatures and on sweat-rate of resting subjects exposed to the same dry-bulb temperature (36°C) and air movement but to a wide range of absolute humidity accorded with expectation, and transition from partial to complete wetness of skin appeared to be abrupt and occurred at the expected level of absolute humidity (37 mm Hg)

Heat Illness

W P Stamm (U K) discussed the nomenclature and classification of heat illness The present W H O International Statistical Classification contained terms and concepts now archaic, and modifications proposed recently to the Climatic Physiology Committee of the Medical Research Council[2] were handicapped by an attempt to remain within existing W H O framework and coding

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[1] Belding, H S , Hatch, T F *Heating Piping, and Air Conditioning*, 1955, 27 8, 111

[2] Weiner, J S , Horne, G O *Brit med J* 1958, i, 1533

Ellis (U K) read a paper by W S S Ladell (U K) idrotic heat exhaustion. This appeared to be funda- lly an endocrine disorder, as inability to retain salt ater accompanied anhidrosis, but failure of target responses was more likely than a central "stage of ex- on" because treatment with posterior pituitary extract xycortone acetate did not always help J P O'Brien alia), unable to attend, sent his belief that the disorder urely local in origin That facial hyperhidrosis was in the presence of anhidrosis elsewhere, and that the otic areas began to sweat if treated with anhydrous , were points which seemed to discount a hormonal

Guthrie (Kuwait) reported that heat illness, usually yperpyrexia and salt and water depletion syndromes, had h higher incidence among oil-tanker crews in the Persian than among those living and working ashore in Kuwait was due to lack of adequate air-cooling on shipboard, unsuitable habits of the sailors exposed. Some 20,000 lets, in eight languages, offering simple instructions in tion of heat illness had been issued to ships calling at it, this appeared to have had good effect, as marine cases sed there in the past three years numbered 222, 137, 3

P Crowden (U K) wished for a wider use of simple res to ensure health in the tropics Whitewashing the or of a corrugated-iron structure reduced the tem- re within When cotton mosquito nets, the meshes of were often occluded by fibrils, were applied to a hospital ur velocity over a possibly febrile patient was reduced to hth of its former level, but synthetic fibre mosquito net- ld not have such a major disadvantage Bright metallic es such as were afforded by aluminium foil had a high tivity and low emissivity for radiant heat, and were there- f value in heated industrial spaces

Toor (Israel) described experiments on two groups ly acclimatised men in the Dead Sea area[3]

Minard (U S.A) discussed prevention of heat casualties g Marine Corps recruits training at Parris Island, South lina. Changes in hot-weather training regulations for included adoption of a heat-stress index based eighted readings of dry-bulb, wet-bulb, and globe- nometer readings (wet-bulb,globe-temperature index of ou[4]) This index was chosen because of the simplicity of nstruments involved Use of the index to modify or restrict ing of recruits at certain levels of heat stress reduced heat lties from 12 4 per 10,000 in 1955 to 4 67 per 10,000 in

Nutrition

ne of the major problems of tropical countries is mal- tion in the young

Bassir (Nigeria) reported that the addition of soy- flour to the maternal diet had a beneficial effect on the position and volume of breast-milk

A Roels (Belgian Congo) had noted that in African hers on a staple diet the protein content of breast-milk during the first three months of lactation, that there correlation between the vitamin-A, carotene, and fat ent, and that there was no relation between content and me of breast milk

he changes in the blood picture in kwashiorkor in the four weeks under treatment were described by F Walt th Africa) Over 60% of children with megaloblastosis he bone-marrow were found to have kwashiorkor, and all cases responded within ninety-six hours after injection lic acid Sudden severe falls in hæmoglobin level had been rved in cases of kwashiorkor with sudden acute infection, pite a constantly rising serum-protein level

G Fuhrmann (Germany) described how his modification of the "arm-girth, depth-of-chest, and width-of-hip" index went some way to solve the difficulty of accurately assessing the state of nutrition

K Hill (U K) stated that infection or malnutrition or both are usually necessary for the development of veno-occlusive disease of the liver in response to ingestion of pyrrolizidine alkaloids

G Moretti (France) had studied the enlargement of the parotid gland in cases of alcoholic cirrhosis in France and of malnutrition in Guinea The histological picture in the two types was similar except that in the African cases interstitial fibrosis was a notable feature

H A P C Oomen (Netherlands) reported his studies in Indonesia on the response of the eye to malnutrition Besides xerophthalmia, retrobulbar neuritis was very common, and though vitamin A was very important the part played by protein and fat in the well-being of the eye must not be forgotten

An interesting condition of calcification of the pancreas in persons aged 15–30 in Indonesia was described by P J Zuidema (Netherlands) The patients required large amounts of insulin, had no steatorrhœa and no ketosis, but frequently had cataract Such cases seemed to be the result of malnutrition, the calcification of the pancreas having been preceded by fibrosis

Experimental aspects of tropical malnutrition was discussed by B S Platt (U K), who described his observations in pigs, in which a low-protein, low-carbohydrate diet produced a greatly different response to a low-protein intake high-carbohydrate diet

Trypanosomiasis

R B Heisch (Kenya) announced the successful isolation of *Trypanosoma rhodesiense* from the bush buck and its transmission to two human volunteers

Hæmoglobinopathies

C Trincão (Portugal) described the methods of identifying abnormal hæmoglobins The principal technique was that of electrophoresis, but there were many others—chromatography, determination of solubility, resistance to denaturation by alkali or by cold, oxygen saturation, aminoacid composition, number of NH_2 and SH endgroups, and antigenic properties Electrophoresis could be carried out at varying pH, by the open boundary technique, by zone electrophoresis on starch paste, starch gel, and agar, and by using various filter-papers or cellulose acetate as the supporting medium

H Lehmann (U K.) described the principal disorders The most severe were the homozygous conditions thalassæmia major and sickle-cell anæmia, milder were the heterozygous thalassæmia minor and the homozygous states for hæmoglobins C, D, and E Intermediary were mixed syndromes in which one gene for sickling and one for thalassæmia were inherited together or either of the two with that for another abnormal hæmoglobin. Additional stress such as pregnancy or infection could acerbate the less severe conditions so that the clinical condition resembled that of thalassæmia major or sickle-cell anæmia In the world distribution of these abnormalities sickle-cell hæmoglobin overlapped the distribution of thalassæmia and hæmoglobin C, and thalassæmia was also common in Asia, where it contributed to the high incidence in some regions of hæmoglobin-E/thalassæmia and in a not yet fully understood way to hæmoglobin-H disease

N C Ferreira (Portugal) said that the fœtal hæmoglobin in thalassæmia was indistinguishable from that in normal infants

R J Cabannes (Algiers) had found high incidences of hæmoglobin C in the High Volta, French West Africa In certain regions there, 17 2% of the people were hæmoglobin-C trait carriers (AC) and 1 3% were homozygotes (hæmoglobin-C

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te *Lancet*, Sept 13, 1958, p 579

aglou C P Annual report no 9 to Commission on Environmental Hygiene, U S Armed Forces Epidemiological Board disease) The heterozygotes were completely normal, and the homozygotes were comparatively little affected, though there was some anæmia and occasional pains in the joints and the abdomen with gastrointestinal upsets There was some lability of the nervous system, which could be demonstrated in the encephalogram Hæmoglobin K was commoner in North Africa amongst the Kabyles and was found only occasionally in West Africa

Lie Injo Luan Eng (Indonesia), in a paper read on her behalf, said that both thalassæmia and hæmoglobin-E/thalassæmia were seen regularly in Indonesia These two were similar in their pleomorphism Whether splenectomy had any therapeutic value was as yet not decided Hæmoglobin-E disease was a *mild* hæmoglobinopathy, and the hæmoglobin-E trait caused no symptoms In some people the hæmoglobin-E trait was associated with microcythæmia and with an increased resistance of the red cells to osmotic lysis

A R **Nogueira** (Portugal) reported on the abnormal hæmoglobins of Portuguese East and West Africa In the East only sickling was found, but he could not confirm reports of some British workers who had described a very high incidence of sickling from Mozambique In the West, Angola showed sickling *only*, but in Portuguese Guinea 14 instances of hæmoglobin N and 11 of hæmoglobin K had been found among 9224 samples Some 20 samples containing a G-like hæmoglobin were still awaiting final identification

F B **Livingstone**, W **Zuelzer**, A R **Robinson**, and J V **Neel** (U S A) reported that some rare hæmoglobins—notably hæmoglobin N—were more frequent in Liberia than elsewhere In some regions of Liberia they had also found patients with classical thalassæmia and also a thalassæmia or thalassæmia-like condition where adults possessed high proportions of hæmoglobin F without their red cells showing the morphological features of thalassæmia

A **Woodruff** (U K) reported on the results of work where blood had been taken from patients with sickle-cell anæmia, "labelled" with radioactive chromium, and reinjected Following the fate of the radioactive cells it was found that there were two groups, one, amounting to about a third, was very short lived and disappeared in about four days, whereas the life-span of the remainder was only moderately reduced By scanning the body surface with a scintillation counter it was possible to show that most of the cell destruction took place in the liver

J P **Jonxis** (Holland) gave an account of the techniques employed in his laboratory for the recognition of the abnormal hæmoglobins In sheep there were differences between the oxygen-saturation curves of two adult variants So far no such differences had been noted in man Even fœtal hæmoglobin did not differ from adult hæmoglobin in that respect—provided that it had been freed from stroma and been thoroughly purified by dialysis Some hæmoglobinopathy-like conditions in which it had not been possible to find an abnormal hæmoglobin by current methods might turn out to be associated with abnormal oxygen affinity of the hæmoglobin

A I **Chernoff** (U S A) in a large survey, had found in North Carolina not only hæmoglobins S and C, but an appreciable number of samples with various "fast"-moving hæmoglobins Hæmoglobin D was present in 1% of American Negroes

L W **Diggs** (U S A) presented very full evidence that sickle-cell disease was a veno-occlusive disorder, the lesions occurring where blood was least oxygenated He demonstrated the development from infarct by sickled cells to necrotic lesion and to repair by organisation in virtually all organs and all parts of the body The spleen was most consistently affected Other characteristic injuries were aseptic necrosis of the head of the femur and occlusive lesions in the periphery of the eyeground The sickle-cell-trait carrier was not immune, he could suffer from splenic infarct when flying at high altitude in non-pressurised aircraft, and there was a specific *hæmaturia*

J C **White** and G H **Beaven** (U K) had compared t current methods of estimating fœtal hæmoglobin Equa good results were obtained with them all, provided the co centration was above 5–10% They improved the sensitivity fœtal-hæmoglobin estimation by combining the alkali d naturation of the non-F hæmoglobin with the measureme of hæmoglobin F in the residue Hæmoglobin F amounted 80 ± 10% at birth, and was less than 10% at four to months Traces could be found up to five years Values up 20% were found in sickle-cell anæmia and up to 90% thalassæmia *major* *Half of the cases of thalassæmia minor* of sickle-cell trait showed traces of fœtal hæmoglobin

J H **Walters** and H **Lehmann** (U K) had examin liver function in sickle-cell anæmia There was progress deterioration with increasing age This was reflected in a r of the serum thymol-turbidity units and in a fall of the pseud cholinesterase level Liver-biopsy specimens showed sinuso filled with a network of silver-staining organic material wh tended to form layers on the walls of the sinusoids

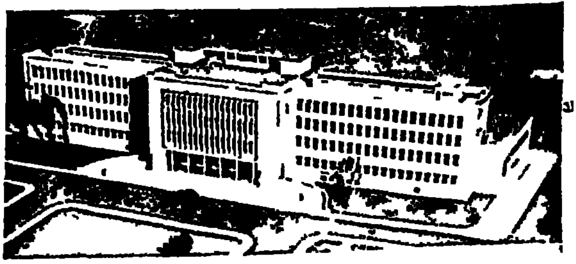
At a round-table discussion a resolution was prepared for t final plenary session of the congress

> "It is recognised that the hæmoglobin diseases present a m *health problem in the countries where they are found—most of th* tropical Millions of people are affected in Europe, Asia, Africa, a the Americas With the expected decrease of infectious diseases t importance of genetical disorders—amongst which the hæmogl binopathies are foremost—*will become greater rather than less* The encouragement is desirable of surveys of the distribution thalassæmia and of the abnormal hæmoglobins Though much h been done, there are still wide gaps in our knowledge Without su information planning of public-health measures will be handicapp With the rapid rate of discoveries of new hæmoglobins and n disorders a real risk arises that the nomenclature of these hæmoglobi *and the terminology of these disorders become confused* T gathering of workers interested in the hæmoglobinopathies hopes t sooner rather than later steps will be taken to arrive at internatio agreement As regards the terminology of clinical disorders cog sance is taken of the 'Recommendations' prepared by the Colo Medical Research Committee Working Party on Sickle-Cell Tr and Sickle-Cell Anæmia, London published in *The Lancet* a *British Medical Journal* on May 25, 1957"

INSTITUTE OF TROPICAL MEDICINE

The new home of the Institute of Tropical Medicine occupies commanding position near the Feira das Industrias Portugesas, the Avenada da India, on the banks of the Tagus

The white stone building is flanked by sculptured symbolic figure and in its wide approach stands a statue of Garcia de Orta, t Portuguese Hippocrates who published his great work on India 1563 Its six floors offer ample space for teaching and research The



two large air-conditioned amphitheatres, which can each seat 12 students, are equipped with head-phones and projection apparatus o all kinds The three laboratories each provide working space for 6 students and independent tables for each The institute has the following departments hygiene and climatology, entomology and helminthology, dermatology *and mycology*, and bacteriology and virology There is a special service for radioisotopes

A special number of the annals of the institute has been published to mark the occasion It gives a full history of tropical medicine i Portugal It describes the schools of Goa, India, Loanda, Angola, Lourenço Marques, Mozambique It shows the range of work o the institute's activities, which extend from Timor in the Indonesia Archipelago to the Cape Verde Islands

In England Now

A Running Commentary by Peripatetic Correspondents

SOCRATES ON MEDICAL EDUCATION*

Alcibiades Tell me, Socrates, how can we be sure that our ctors are well trained?

Socrates Do you think it right, Alcibiades, that we should r of a pudding that it is good or bad?

Alcibiades Certainly, Socrates

Socrates It must be possible then to distinguish a good dding from a bad one?

Alcibiades Of course it is, Socrates

Socrates And I suppose you would say that a good pudding ist have good ingredients?

Alcibiades That is so, Socrates

Socrates Tell me, Alcibiades, which ingredient do you think most important?

Alcibiades I think the flour is, for without the flour there ıld be no pudding

Socrates And whom do you consider the best judge of flour?

Alcibiades I suppose the farmer, who grows the wheat, can ıt tell which is the best flour

Socrates And would you say the miller also has this knowlge?

Alcibiades Yes, the miller also

Socrates So it would follow, would it not, that the farmer d the miller are amongst the best judges of what is a good dding?

Alcibiades It would seem so, Socrates

In like manner Socrates persuaded Glauco to say that the ultry-keeper must judge the eggs, and Agathon that the vinerd owner knew most about the raisins

Then Apollodorus broke in But Socrates, you have fortten the honey!

Socrates I was coming to the honey, Apollodorus, but tell why you think it important.

Apollodorus It gives sweetening and flavour to the whole idding, Socrates Why, half the pudding is the honey

Socrates That would surely mean putting a great deal of ney into a pudding!

Apollodorus I do not mean half by weight, but through its vasiveness honey is the other half of the pudding

Socrates How then would you judge the honey, Apollodorus? ould an Athenian who keeps bees be a suitable judge?

Apollodorus No indeed, Socrates, for he does others things sides keep bees The judge of honey must be a member of bee-keepers guild from Hymettus

Socrates Well, when you have judged the ingredients there still the mixing in the right proportions and the cooking at right temperature Would you include a cook amongst your idges?

Eryximachus Yes, Socrates, we must include a cook, but we ust be careful not to choose the one who cooked the pudding is well known that if a prize of 100 drachmæ were to be warded for the best pudding no cook would think his own udding worthy of less than 90 drachmæ

Socrates Where, then, would you find a cook to judge your udding?

Eryximachus If it is an Athenian pudding, to be on the safe ide you must choose a cook from Sparta

Socrates But what will happen if the Spartans do not like the ame kind of pudding as the Athenians? And do you think, lcibiades, that all your judges will agree about the pudding? r will the farmer, perhaps, say that his good flour has been poiled in the mixing, and the raisin-grower that there is too uch honey?

Then, turning to a boy who was sitting at his feet, Socrates nd Boy, you have heard what Alcibiades and the others have id. How would you decide whether a pudding is good or ad?

Boy I would eat it, Socrates!

For a congress on tropical medicine there could hardly be a more appropriate venue than Lisbon with its long history of adventure and exploration The hospitable Portuguese had rushed ahead with their new institute of tropical medicine, so that we could meet within its walls, though some of the rooms had not been finished Indeed when we first arrived workmen were surging around with buckets of cement The film room, which hardly existed on Sept 4, was complete and in working order on the morning of Sept 5 The main staircase had only been put in place four days before, and a gang of a thousand navvies worked all night to get the building ready for the congress

Behind the information desks sat Portuguese ladies who, though sometimes a bit puzzled, were always most helpful, and we soon came to learn why these people are acknowledged as the kindest and most considerate in the world. Typical of their friendly and charming hospitality were the attractive stamps issued to commemorate the Congress, which showed gaily coloured birds, flowers, insects, and mammals from the Portuguese tropical possessions At our meetings, social and scientific alike, everyone was pleased to meet everyone else, had something to impart, or questions to ask It may well be that we all had diverse blood-groups or harboured different brands of hæmoglobin, but the antigen of good will was common to all

* * *

A student of art learns to look for the characteristic touches of the master He knows that certain themes recur frequently—perhaps the pattern of light thrown by a candle, or the gables of a house viewed from a characteristic angle The same is true in science, and when this year I began to review half a century of progress in cardiac physiology I found that I recognised not only the style and mannerisms of some authors over the years, but sometimes also their hopes, their disappointments, and their regrets There is a poignancy in the way they return to an idea or concept, born of some ancient intellectual anguish but fated by hard facts to die It is almost as if they hope yet to detect life where there is none

The ancient journals, too, have a strange, nostalgic fascination. It is a privilege to lift the veil and listen, even if rather indistinctly, to men like August Krogh or Lindhard or Yandell Henderson, and how interesting it is to find that the views some of my older contemporaries express today found origin in ideas and concepts that they lived with, as only a scientist worrying out an idea can live, perhaps thirty years ago

* * *

My partner, who has only been two years in general practice, remarked the other day that really important statements by patients or their relations are often made on the doorstep on departure

My mind must have registered this too, without having put it into words, for it at once accepted the truth of the observation If I needed confirmation it came at once The next day as I was leaving the house of a man with depression and dyspepsia, who refused to own up to any worries or reasons for nervous tension, a married daughter saw me to the door and literally on the doorstep said, "You know, my sister wants to get engaged, but father so dislikes the idea of losing his youngest daughter that he won't even meet the young man."

The incident that had struck my partner so forcibly was his visit to a child with the mildest of sore throats As he was leaving the mother said, "By the way, doctor, my husband is coughing up blood, but he won't tell you himself"

* * *

A colleague practising in a Yorkshire mining town describes his most embarrassing moment Called in to give a supporting certificate for cremation, he did his duties quietly and speedily and expected that the undertaker would be equally circumspect, and would forward the prescribed fee later on

A few days later he stood to attention in the High Street as a funeral procession crawled by Suddenly the leading vehicle swerved across to where he stood and a hand poked out towards him "Your £2, doctor—saves a stamp," said the top-hatted and black-coated driver, who then resumed his place at the head of the dignified procession

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*The first meeting of the Association for the Study of Medical Education is being held in London this week.

Letters to the Editor

THYMECTOMY AND MYASTHENIA GRAVIS

SIR,—There are many arguments against the likelihood of thymectomy benefiting sufferers from myasthenia gravis The only justification for attempting the surgical experiment was the enlargement of the gland in some patients and the presence of a " thymoma " in a number of others It has to be admitted, however, that a majority of patients have a thymus that is normal in every respect, and, again, a thymoma does not necessarily lead to myasthenia Removal of the thymus is followed by no *symptom whatever, no recognisable syndrome of hypo*-thymism This suggests surely that the function of the thymus, if any, is duplicated by other organs and that this gland is comparable in this respect to the spleen rather than to any known endocrine gland

When we come to the results of thymectomy, recently assessed by Simpson [1] and discussed in your excellent leading article of Sept 6, we find some very puzzling features The operation benefits women, but probably not men The worse results are to be expected when the most abnormal glands, the thymomas, are removed, although an excellent result is sometimes seen in this category of patients and indeed often follows removal of apparently normal glands The chances for the myasthenic to remain in status quo, operation or no operation, are about the same If men, children, and the bearers of tumours are excluded and assessment is focused on a special class, women between 16 and 35 years old, then we find a distinct advantage for surgery

My knowledge of the statistical method does not allow me to judge how far it is fair to separate and select groups of patients in this way Assuming the favourable response of some young female patients to be proven, I would like to refer again to a suggestion I made some years ago [2] I said then, " Can it be that myasthenia gravis is a label covering a number of disorders of the myoneural junction ? Every functional unit of the neuromuscular system has its own varied pathology Is it not, a priori, likely that the myoneural junction can be impeded in more ways than we know ? "

Suppose that an enterprising surgeon, fifty years ago shall we say, had decided for splenectomy in every obscure case of anæmia, as this organ was often known to be enlarged, would he not have had some remarkable results —for instance, in a group of young subjects with a familial incidence of anæmia ?

London, W 1 L P E LAURENT

THE NATURE OF THE INSULIN-ANTAGONIST ASSOCIATED WITH PLASMA-ALBUMIN

SIR,—We have recently shown that the inhibitor of insulin in the plasma of diabetic patients is associated with the albumin fraction Furthermore it was shown that albumin from normal subjects also has an inhibitory action [3] These studies gave no indication of whether such an inhibitory activity was due to the albumin per se or was due to a substance associated with it We now wish to present evidence that the latter is the case

Effect of Hypophysectomy

Three hypophysectomised patients have been studied Two of the patients had carcinomatosis and had their pituitary *ablated by transnasal implants of yttrium-90* into the sella turcica These patients were cortisone-dependent The third patient was diabetic and the pituitary gland was removed by surgery, which was easy and complete Albumin was prepared by the trichloroacetic-acid/ethanol method from the plasma of these patients and tested for insulin antagonism by the rat-diaphragm technique as described in our last paper [3] The plasma-albumin fractions from all these patients had no demonstrable antagonistic activity The albumin fraction in each case was tested at least twice The results which have been taken together are shown in the accompanying table In one case it was possible to determine the activity of the albumin fraction before operation and as expected this fraction was inhibitory

ACTION OF ALBUMIN FROM NORMAL, HYPOPHYSECTOMISED, DIABETIC SUBJECTS

Fraction	Mean glucose uptake above basal ± standard error of the mean (mg per 100 ml per 10 mg diaphragm)	
	Buffer + 1000 microunits per ml insulin	Fraction in buffer + 1000 microunits per ml insulin
Normal albumin (3 5–5 5%)	11 43 ± 0 62 (6)	0 50 ± 0 48% (6)
Hypox albumin* (4%)	11 85 ± 0 68 (8)	11·43 ± 0 80 (8)
Diabetic albumin (1 25%)	12 32 ± 1 04 (4)	3 55 ± 0 67 (4)
Diabetic albumin through column (1 25%)	*13 12 ± 0 65* (6)	*12 58 + 1 28* (6)

No of observations in parentheses

*Hypox albumin represents albumin isolated from the plasma of hypophysectomised patients

Removal of Activity on Columns of Cellulose

Albumin from diabetic patients (300 mg) was prepared, with the activity previously described,[3] dissolved in 4 ml of borate-phosphate buffer, and passed through a column (40 cm × 1 5 cm) of cellulose [4] The protein was eluted with buffer and a total of 150 ml of buffer was collected, the eluent extensively dialysed and the protein freeze dried When the activity of this protein, which was electrophoretically identical with albumin, was tested, the original activity against insulin was found to have been removed by passage through the column The results are shown in the table A similar result was obtained when 750 mg of normal albumin was passed through a column under similar conditions

Together, both these lines of evidence indicate that the activity of the albumin fraction from normal subjects and diabetic patients against insulin is not due to albumin per se The results of hypophysectomy indicate that the antagonistic activity is related, possibly indirectly, to the pituitary gland This gland may not be solely responsible, however, as is suggested from studies on experimental diabetes in animals Thus in depancreatised cats the presence of insulin antagonism in the plasma is dependent both on the presence of the pituitary gland and on adrenalcortical steroids [5] These results are in accord with those of Luft et al [6], who showed that the insulin requirements of diabetics who had been subjected to hypophysectomy fell as the result of the operation

We should like to thank Prof Russell Fraser and Dr J D N Nabarro for allowing us to study patients under their care, the Medical Research Council for a grant for scientific assistance, and Boots Pure Drug Company for supplies of recrystallised insulin

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J VALLANCE-OWEN
ELIZABETH DENNES
P N CAMPBELL

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1 Simpson J A *Brain* 1958, 81, 112
2 *Brit med J* 1949, ii 814
3 Vallance-Owen, J , Dennes, E , Campbell, P N *Lancet*, 1958, ii, 336
4 Campbell, P N , Stone N E *Biochem J* , 1957, 68, 19
5 Vallance-Owen, J , Lukens F D W *Endocrinology*, 1957, 60, 625
6 Luft, R , Olivecrona, H , Ikkos D , Kornerup, T , Ljunggren, H *Brit med J* 1955, ii, 752

SKIN TRANSPLANTATION IMMUNITY IN RELATION TO HYPERSENSITIVITY

SIR,—Reading, with appreciation, the preliminary unication of Sept 13 by Professor Medawar and colleagues, I was left uncertain as to the nature of the terial obtained from the cells expressed from the phoid tissue of the recipient animal and injected in " direct reaction "—presumably mitochondria and osomes (R N A, granules), amongst other things

Professor Medawar at one time produced evidence ch indicated that there were tissue antigens in cell clei On general principle, it seems improbable that ue antigens or, to use Loeb's more descriptive term, erentials are the exclusive property of any particular extract or fraction More likely it is an attribute pervading all living macromolecular systems in the higher animal form and resides in characteristic molecular configurations The proteins, with a choice of over twenty aminoacids offering an infinite number of positions all the possible side-groups and linkages, could provide a sufficient range of molecular pattern for all tissues, viduals and species One wonders, therefore, if borate procedures and processing of living tissue adds anything to the problem of homograft reaction

Department of Anatomy,
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G M WYBURN

SPHINCTER AND HIATUS

SIR,—An interesting aspect of the hiatus-hernia problem, so far not mentioned in your review of this fascinating subject, is whether or not so-called " sliding " hiatus hernias commonly slide

Belsey [1] has stated that they rarely slide to and fro through the hiatus, the radiological appearances being an illusion However, so long as it is generally accepted that a hernia may come and go spontaneously, the radiologist has an excuse for not demonstrating the lesion regularly when it is present, and moreover will tend to be preoccupied with manœuvres designed to promote reflux and/or herniation It is a common experience that repeated barium examinations are at present necessary in a proportion of cases

Rejecting this assumption immediately puts the radiologist on his mettle to improve the present unreliable technique In this respect the image intensifier offers hope for the future, with its use gastric-type mucosal detail may often be clearly seen above the diaphragm as the barium bolus passes, even in the erect position

Supposing that the hernial pouch is permanently fixed above the diaphragm and that the pressure within it approximates to that within the intra-abdominal stomach,[2] then support for the action of the external mechanisms acting at the hiatus in preventing reflux into the pouch during barium-meal examination, is provided by the following simple experiment

If a baby's feeding-bottle is inverted with the neck of the teat partially constricted (by compression or angulation), then the bulb will not fill completely with fluid because an air-bubble is present In the case of a hiatus hernia, this mechanism would probably act as a complete or partial air lock, the air being prevented from escaping upwards by the alleged internal sphincter or by a more diffuse contraction of the lower œsophagus, as mentioned previously [3] Complete occlusion of the neck of the hernia at the hiatus would be unnecessary, which would account for the rather unimpressive pressure changes found here

Belching would tend to lose the air and so promote reflux Donnelly [4] has related the formation of a hiatus hernia and reflux symptoms to this habit

Southmead Hospital,
Westbury-on-Trym,
Bristol

E A W HOUGHTON

BREAKING UP THE MENTAL HOSPITAL

SIR,—Although broadly agreeing with the views expressed by Dr Russell Barton (Sept 13), we feel that the topic is of such importance that it deserves further ventilation

Anybody who studies the history of psychiatry will find that from time to time during the last 100 years the same ideas on treatment have been dressed up in new clothes and put forward as a sure solution of the problems confronting mental hospitals This applies particularly in the field of *administrative* psychiatry where we now hear repeated pleas for the doors to be thrown open and the patients discharged to the tender and loving care of their relatives We also find a resurgence of the idea of community care, domiciliary treatment, and indeed complete abolition of the mental hospital

With the *medical* problem of psychiatry in its present state of flux, it is as well to view any of these new advances with a critical eye For example, nowadays the old concept of the hospital farm, where chronic patients could work, is considered outmoded and many hospital farms have been closed as uneconomic This idea has now been replaced by the plea for factories to be established in mental hospitals Are they to be more economical ? Some years ago large observation wards attached to general hospitals were instituted as an administrative solution to many problems in industrial cities such as Glasgow and Manchester Today this idea is discredited because these wards have failed to cope with the disposal of chronic cases Nevertheless, psychiatric departments in the general hospitals are suggested as a panacea against institutionalisation by some reformers The situation would not seem to be very dissimilar to that which prevailed in the treatment of tuberculosis before the advent of modern effective chemotherapy Some saw the solution in extensive village settlements, others through the provision for outpatient dispensaries, &c , in fact, the real advance has had to wait the advent of an effective medical rather than administrative treatment Administrative changes in psychiatry are required and may indeed be helpful, but we should like to make a plea for a degree of self-criticism which is not often apparent in those who conduct these so-called new experiments

We disagree with the views expressed in Dr Barton's article about institutional " neuroses " The features of apathy and indolence so often seen in chronic schizophrenics are essentially a product of the disease itself and, like aggression and hostility, not infrequently seen in schizophrenics who have lived outside a hospital all their lives, as we tried to demonstrate in our description of the chronic patient in India [5]

The enthusiastic and sometimes incautious discharge policy of some hospitals can indeed have tragic repercussions on the family

A case recently seen by one of us had passed through the hands of a mental hospital near London where a man in his fifties had been under care and treatment for the past ten years The hospital discovered that the patient had a sister in her seventies living near Birmingham and wrote to her that the patient was now well and was to be discharged under her care, no other preparations for the transfer were made The results were disastrous, the still psychotic patient nearly drove his sister to a breakdown and had to go into hospital in Birmingham This case is by no means an isolated example, and we frankly admit that we have seen equally bad effects on the family of some of our own patients we have attempted to discharge from hospital

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[1] Belsey, R in Modern Trends in Gastro-enterology London, 1952
[2] Atkinson, M , Edwards, D A W , Honour, A , Rowlands, E W *Lancet*, 1957, ii, 1138
[3] *ibid* Sept 6, 1958, p 525
[4] Donnelly, B *Brit J Radiol* 1953, 26 441
[5] Mayer-Gross W , Cross, K W , Harrington, J A , Sreenivasan, U *Lancet*, 1958, i, 1265

Psychiatrists battling with a human problem of the greatest practical difficulty are certainly not immune from self-deception, but neither are experts in social medicine, nor our Great Planners and Medical Politicians A lack of critical evaluation of what we are trying to do often leads to an overactivity in the wrong direction and to a repetition of past errors

Uffculme Clinic,
Moseley, Birmingham

W Mayer-Gross
J A Harrington

Sir,—*The letter from Dr Russell Barton raises a* number of relevant questions

We know that some of our discharged patients have entered other hospitals, just as we admit patients who have been treated elsewhere Nevertheless, it is our impression that more patients move into our area than out of it This impression is strengthened by our social worker's reports and is in keeping with the fact that schizophrenic patients tend to be found in excess in the central areas of towns [1,2]

I am indebted to Dr Walk of Cane Hill Hospital, who has allowed me to see some figures he has collected from the Coroner's courts of South London These show that in 1956 and 1957 the number of ex-patients from Banstead who committed suicide was less than half of that for the other comparable hospitals

Contrary to Dr Barton's statement, we do not know of any mental hospital which is willing to take patients from our area Moreover, we have had referred to this hospital a number of patients from outside our area They were referred to us because of our policy of active treatment in an optimistic atmosphere

We are, of course, particularly concerned that discharged patients should not cause distress in their homes Apart from a general awareness of this risk, we have had a research scheme running for nearly three years, which is concerned with the social problems of schizophrenic mothers This group was chosen because it was thought it would highlight the problems of patients returning to the community It is apparent that all these patients have difficulties on leaving hospital—sometimes severe In general however, once overt symptoms have been treated, the longer the patient is away from home, the greater the difficulties the whole family will experience when attempts are made to re-unite them Once the optimal time has passed, families tend to organise their lives without the absent member

I entirely agree that institutional neurosis can develop in small wards as readily as in large, and the most important factor in curing this condition is the spirit which animates the staff It is difficult to see how a mental hospital can provide full after-care facilities without becoming unwieldy I would agree with Dr Barton however if he means that such facilities in the community should be supervised from the mental hospital

Banstead Hospital,
Sutton Surrey

A A Baker

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[1] Faris, R. E L, and Dunham, H W *Mental Disorders in Urban Areas* Chicago, 1939

[2] Hare, E. J *J ment Sci* 1956, 102, 349

INDUSTRIAL MEDICINE AND GENERAL PRACTICE

Sir,—I should like to support Dr Keatinge (Sept in questioning Lord Taylor's contention that "a part of industrial medicine is neither more nor less general practice" The latter is freely assumed by people to be the only form of medical activity (other hospital work) undertaken by doctors, and when eminent authority emphasises this feature, it mak increasingly difficult for industrial medical officers to suade managements and employees that this is not case

In discussing broad issues generalisations are a sary evil, but I think few will disagree with the stat that the general practitioner mainly directs his effor the detection and treatment of disease while the medical officer is mainly concerned with the *relatior* between disease (or disability) and occupation relationship may find expression in three ways

(1) *Causation* disease or disability directly of origin

(2) *Aggravation* where conditions of work make wor disease or disability already present

(3) *Interference* where the disease or disablement feres with the ability of the employee to do his work

These aspects of the relationship between disease occupation may appear singly or together Whatever is case, the efforts of the industrial medical officer are directe removing, ameliorating, or otherwise adjusting the rel Ideally the relationship should exist in theory only, preventative medicine truly would have been done

If this simple conception of an industrial officer is kept in mind then there will be no confusio to whether he "practises generally"

Before I am attacked on all sides I should like to that the provision of emergency treatment for accid and illness is a vital part of his work but it should in way be regarded as the paramount reason for his existe in industry

Medical Department,
Stewart and Lloyds,
Newport, Mon

G Thomas

TRIALS OF CONTRACEPTIVES

Sir,—This Council is trying to organise clinical tr to test the efficacy of existing methods of contracepti We are also hoping to try modifications of these meth and ultimately, we hope, entirely new methods will tested in the same way

To establish any new method of contraception ne volunteers who are willing to run a reasonable risk becoming pregnant, and who are also likely to be fert We have in fact two groups of trials running at present

Group 1, in which the volunteers use the method for fr 3 to 12 months and then prove both its effectiveness and th fertility by becoming pregnant, and group 2, in which vol teers use a method for about a year, being prepared to run risk of its failing but not being prepared to undertake pregnan There is also a third trial in which patients are medically se and examined at a special clinic session in London Grou and 2 patients are not seen unless the patient-volunt specifically wants to be seen

In view of our lack of accurate figures about t effectiveness of modern contraceptive methods a because of the importance of this problem both individual families and to world population trends we f that the trials are of vital importance

If any of your readers can put us in touch with volunteers who should write to the medical secretary at this address) e would be most grateful

G I M SWYER
Chairman
H B WRIGHT
Secretary,
Technical Subcommittee

Council for the Investigation
of Fertility Control,
64, Sloane Street,
London, S W 1

HÆMORRHAGIC PLEURAL EFFUSION AS A MANIFESTATION OF SCURVY

SIR,—Dr Rozner and Dr Lloyd (Aug 23), in their teresting article on scurvy, quote Lind (1753) for an early description of pleural involvement I should like to call attention to Jacques Cartier's *Brief Recit* of 1545 in which he describes the postmortem findings of a case of scurvy in Canada in the year 1535

> "Because of our ignorance of the disease, the captain had the body opened to obtain whatever knowledge of it might help to preserve the rest of us if possible The heart was found white and wrinkled, with nearly two quarts of reddish, date-coloured water about it The liver was healthy but the lungs were all blackened and mortified and all the blood had collected above the heart, for when the body was cut open there issued from above the heart a large amount of dark, putrified blood The spleen, for two finger breadths near the backbone, was likewise a little affected, as if it had been rubbed on a rough stone These facts having been noted, one thigh was cut open and found very black outside but with fairly healthy flesh inside" (From the translation of Prof Jean L Launay)

Charles E Frost & Co,
Montreal

J M. PARKER
Pharmacologist.

CONTROL OF THE COMMON COLD

SIR,—Over a period of years, it was noted that quite unexpectedly good results were being given by prophylactic autogenous vaccines in the prevention of the common cold It seemed reasonable to assume that the function of the virus was essentially that of a starting handle, most of the later and debilitating symptoms being due to the patient's own nasopharyngeal bacteria which became out of hand as a result of the general depression due to the virus [1]

If so, a similar result should be obtainable by short-term local antibiotic therapy at the start of the symptoms, thus depressing the activity of the bacteria to correspond to the general depression of the patient A series of experiments was therefore carried out during the winter of 1956–57 The result confirmed expectations, in that use of the appropriate antibiotic at the onset considerably reduced the number of fully developed colds [2]

During the winter of 1957–58, a further trial was made on exactly the same lines as that of the previous winter, essentially as a check to ensure that the highly promising results achieved were not due to chance in any way The results are given in the accompanying table

The proportion of volunteers with prodromal symptoms who went on to a full cold was again much lower in the treated than in the control group As in the previous series, lateness in reporting prodromal stages proved disadvantageous, but this trial was intended to be a practical one and the figures therefore include all comers

From October, 1957, until May, 1958, 1120 volunteers were divided into two groups Of these, 838 received short-term antibiotic treatment when they felt a cold beginning, and 282 received an inert tablet In the treated group, prodromal stages numbered 304 (36 3%) of which 52 (17 1%) went on to full colds In the control group, the prodromal stages numbered 121 (42 8%) of which 64 (52 9%) went on to full colds—i e, 6 2 colds per 100 volunteers in the treated and 22 7 per 100 in the control group

Allowing for the fact that latecomers (i e., those reporting prodromal stages after a day or two) were accepted in 1957–58 and largely refused in 1956–57, these figures strongly support the findings of the previous year—4 colds per 100 in the treated and 26 per 100 in the controls For 304 volunteers where such assessment was possible the figure for 1957–58 worked out at 4 8%

The fact that the findings during 1957–58 show such a strong resemblance to those of 1956–57 is evidence that the conclusions put forward, and probably the assumption on which they are based, are correct In that case, the following points arise

(1) *Chronic cold sufferers* —The method of choice here is the autogenous vaccine, giving active immunity A short course of minimal oral antibiotic may if necessary be given to prevent development beyond the prodromal (virus) stage, but this should not be necessary once immunity has developed. A sensitivity test can be recorded when the vaccine is made in case it is required Incidentally, such patients as have had two courses of vaccine appear to have developed a lasting immunity, none ever having been given a third

(2) *The "casual" cold* —This does not warrant a vaccine and should respond to oral antibiotics on the lines indicated In industry, where a medical centre is available, sensitivities can easily be recorded in the early autumn, for use throughout the ensuing winter There is, of course, nothing to prevent

NUMBER OF VOLUNTEERS AND INCIDENTS IN EACH GROUP

—	Works I (aeroplane parts)		Works II (feeding-stuffs)		Works III (rubber tyres, &c.)		Total	
	A	K	A	K	A	K	A	K
No of—								
Volunteers (V)	534	182	228	75	76	25	838	282
Colds (a)	31	39	8	14	13	11	52	64
Improved only (b)	14	2	2	—	—	—	16	2
Prodromal only (c)	118	34	63	17	55	4	236	55
Incidents (a+b+c)	163	75	73	31	68	15	304	121
a a+b+c	31 163	39 75	8 73	14 31	13 68	11 15	52 304	64 121
%	19·0	52·0	10·9	45 2	19 1	73 3	17 1	52·9
c a+b+c	118 163	34 75	63 73	17 31	55 68	4 15	236 304	55 121
%	72·4	45 3	86 3	54 8	80 9	26 7	77·6	45 5
a+b+c V	163 534	75 182	73 228	31 75	68 76	15 25	304 838	121 282
%	30 5	41 2	32	41 3	89 5	60·0	36 3	42 9
a V	31 534	39 182	8 228	14 75	13 76	11 25	52 838	64 282
%	5 8	21·4	3·5	18 7	17 1	44·0	6 2	22 7

A = no of volunteers reporting incidents who received antibiotics.
K = controls receiving inert tablets

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[1] Ritchie, J M *Lancet*, 1958, i, 615

[2] Ritchie, J M *ibid* p 618

practitioners doing the same with patients, but as these do not usually report at the beginning of a cold, the early opportunity is apt to be missed It has been found that, although there is a considerable degree of constancy in the mouth flora, it is better to repeat the sensitivity test each autumn

(3) *Influenza* —Many practitioners have noticed that treating some early cases of influenza with systemic antibiotics, on purely empirical grounds, appears to have reduced the incidence and severity of complications It is perfectly logical to assume that, if the cold virus is essentially a starting-handle, the influenza virus may be the same, albeit on a different scale The continued prophylactic use of systemic antibiotics may lead to the production of resistant bacteria and is therefore to be condemned, but their administration for a few days in an emergency like an imminent attack of influenza is open to no such objection As the result of a sensitivity test can be read after overnight incubation, there is no reason why the antibiotic appropriate to the patient's nasopharyngeal flora should not be used in an attempt to reduce the effects of bacterial invasion, even in cases of influenza

Public Health Laboratory,
Birkenhead
J Morrison Ritchie

HÆMORRHAGIC LESIONS DUE TO STAPHYLOCOCCAL TOXIN

Sir,—The production of hæmorrhagic consolidation of the lungs, in mice, using filtrates of staphylococcal cultures, reported by Professor Ogasawara and Dr Tanaka [1], is an important observation The experiments reinforce the suggestion that fatal hæmorrhagic staphylococcal pneumonia, in man, is due to the production of staphylococcal toxin in the colonised lungs [2] Furthermore they re-emphasise that the rapidly lethal effect of staphylococcal toxin in experimental animals can be prevented by antitoxin, we hope this will encourage further trials of the treatment of acute staphylococcal toxæmia, in man, with staphylococcal antitoxin [3]

It might, however, be unwise to risk aggravating the characteristic systemic hypotension of staphylococcal toxæmia by the use of tetra-ethyl ammonium compounds or by chlorpromazine until there is further evidence of the efficacy of these drugs in protecting the pulmonary circulation from the acute pressor effects of staphylococcal toxin [4]

Department of Pathology,
University of Cambridge
G A Gresham
M H Gleeson-White

COLOUR INDEX IN NORMAL SUBJECTS

Sir,—Dr Pooley (Sept 13) gives values for the colour-index to the nearest 0 01 Such supposed accuracy is surely without meaning, for to be able to estimate the colour-index to within a range of 0 01 the hæmoglobin must be estimated to within ±0 25%, and the red cells to within ±12,500 per c mm

Even the more rational calculation within 0 05 requires a hæmoglobin ±1 25% and red cells ±62,500 per c mm —an accuracy beyond that of a routine hospital laboratory

Briggs and Allington, using the M R C photometer, found a standard deviation of 4 5% for successive hæmoglobin estimations on the same subject, and I have seen a teaching hospital laboratory vary by as much as 10%

I therefore doubt whether there is much practical value in reporting the colour-index to a second decimal place, using laboratory methods at present available

Department of Pathology,
Royal Infirmary,
Blackburn
Keith Horsfield

CHILDREN IN HOSPITAL

Sir,—It is difficult to criticise constructively the letter of Mr Herzog in your issue of Sept 6, as there so much with which a psychiatrist can agree I am sure he is right when he implies that patients over five years, and certainly those over eight years of age, can do with weekly or even less frequent visiting This is especially true when the community atmosphere is highly developed and when all the adults surrounding the children are able make good and happy relationships that are warm and permissive, not cold and punitive, as still happens in some children's wards

It is, however, one of the disadvantages of boarding schools that they weaken family relationships, at least in the pre-adolescent It is imperative that we constantly remember that family loyalty is something far more precious and important than group or national loyalty

With regard to the under fives, and especially to those of two and three years of age, frequent and if possible daily visiting is vital to the proper development of their personality and emotional stability One recognises that at times this may be very difficult and require great sacrifice on the part of parents, and that in some cases it is impossible However, it is our duty to see that parents who *say* they cannot visit frequently are, in fact, not unaware of the intense suffering of small children separated from their parents They should be helped to be made aware of the emotional needs of those small children and then perhaps they will realise that making tea for their husbands coming home from work is not in itself a good reason for staying away Any husband worth his salt can get his own evening meal

Of course, it is not just the frequent contact with parent and child that is important but the depth and quality of their unconscious non-verbal relationship This cannot, of course, be produced by ministerial directives on visiting Where it is deficient it can only be produced by analytically orientated group or individual discussions with parents Sometimes, of course, so malignant are the unconscious forces in a mother's personality that this happy relationship can never be produced

Would not Mr Herzog agree that the child in the film *A Two-year-old Goes to Hospital* suffered? Would he not agree that the clinging and demanding behaviour after that child returned home is at the very least distressing to parent and child? Surely it is our duty to minimise all suffering to the utmost of our limits For those who have eyes to see the film is quite conclusive A recent letter in the *Manchester Guardian* clearly demonstrated the after-effects of a prolonged stay in orthopædic hospitals, which were in essence a permanent and more severe form of those demonstrated by the film

The remark that disturbed me most in Mr Herzog's letter was that "crippled children stand out because of their quiet, non-complaining behaviour" By writing such a statement, he has unwittingly vindicated the work of Dr Bowlby and others Quiet passivity is the depressive picture seen in those who have suffered severely from prolonged emotional deprivation and is particularly seen in many displaced persons who have for years been emotionally starved in concentration camps, a sign therefore of serious maladjustment rather than good adjustment

Might I suggest that Mr Herzog and those who think like him could perhaps find time to study more closely with their psychiatric colleagues the sometimes hidden and subtle effects of hospitalisation

Carlton Hayes Hospital,
Narborough, nr Leicester
H B Kidd

Sir,—I am delighted to read that hospitals are not so bad for children after all I congratulate Miss Stephen and Dr Whatley (Sept 20) on their most enlightened approach to this question

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[1] *Lancet*, Sept 13, 1958, p 589
[2] Gresham, G A, Gleeson-White, M H *ibid* 1957, i, 651
[3] Gresham, G A *Brit J clin Pract* 1958, 12, 247
[4] Burnet, F M, Kellaway C H *Med J Aust* 1930, ii, 295

I suppose we are an enlightened isolation hospital in that daily visiting of children is allowed, together with extra visiting as indicated

Personally I have noted little difference in the behaviour of children. The majority settle down as they always did A few fret and fume, but nine times out of ten they are nly children of elderly or anxious parents

As Miss Stephen and Dr Whatley say, some have actually benefited morally and psychologically from their stay, in particular backward children and those from homes where there is parental discord

Those that are discharged against medical advice do not amount to more than 0 01% of all admissions

Ilford Isolation Hospital,
Chadwell Heath, Essex.

I M. LIBRACH

THE MEDICAL SOCIETY OF LONDON

SIR CECIL WAKELEY, president of the Medical Society of London, writes

"I am writing to crave your assistance in helping this old Medical Society of London to obtain pictures of former presidents We have almost a complete list of presidents of this society since its foundation in 1773, but we have a few gaps ver the years I should be very grateful if any of your readers can help the society by loaning pictures of any of the following

John Millar, M.D , 1773
George Edwards, M.D , 1779
George Pinckard, M.D , 1811
[illegible]omas Walshman, M.D , 1817
[illegible]d Unwins, M.D , 1821
William Shearman, M.D , 1823
John Burne, M.D , 1831
John Whiting, M.D , 1835
Thomas Egerton Bryant, 1837
Leonard Stewart, M.D , 1839
George Pilcher, 1842
Theophilus Thompson, M.D , F.R.S., 18[illegible]
Walter Cooper Dendy, 1846
Edward Headland, 1854
Francis Hird, 1857
William Hughes Willshire, M.D , 1858
Francis Sibson, M.D , F.R.S , 1862
Peter Marshall, 1869
John Cockle, M.D , 1879

I am very keen to see the completion of this permanent record of photographs of all the past presidents"

Diary of the Week

SEPT 28 TO OCT 4

Tuesday, 30th

ROYAL STATISTICAL SOCIETY
5.30 P.M. *Medical section.* (London School of Hygiene and Tropical Medicine, Keppel Street, W C.1) Dr J P M Tizard Prevalence of Mental Defect.

Wednesday, 1st

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 15 P.M. *History of Medicine* Sir Eric Riches A Manuscript of Benjamin Collins Brodie s Surgical Lectures—with Some Notes on the History of Stricture and Stone.
8 P.M. *Surgery* Dr B Marden Black (Mayo Clinic, Minnesota), Mr Vaughan Hudson Present-day Views on the Treatment of Thyroid Conditions (other than Cancer)

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W.3
5 P.M. Sir Russell Brock Surgical Treatment of Pulmonary Stenosis

INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5.30 P.M. Dr R. W Riddell Fungi as Saprophytes and Parasites

MANCHESTER MEDICAL SOCIETY
5 P.M. *Medicine* (Medical School University of Manchester) Dr R. W Luxton, Dr Deborah Doniach Hashimoto s Disease.

Thursday, 2nd

ROYAL SOCIETY OF MEDICINE
5 P.M. *United Services* Dr A. M Joekes Hæmodialysis in Renal Failure and Some Points in the Diagnosis of Acute Renal Failure. Group-Captain R. C. Jackson Experiences with the Kolff Twin Coil Artificial Kidney Dr J E Scott Biochemical Aspects of Hæmodialysis
8 P.M. *Neurology* Dr Hugh Garland Endogenous Hypoglycæmia. (Presidential address)

ASSOCIATION OF CLINICAL PATHOLOGISTS
2 P.M. (Royal College of Surgeons, Lincoln s Inn Fields, W C.2.) Opening of three-day meeting

Friday, 3rd

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Anæsthetics* Dr H J V Morton Demonstration and Deception by Diagram. (Presidential address.)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C.1
3.30 P.M. Dr Norman Hulbert Blood Disorders in Association with Ear, Nose, and Throat Diseases.

Notes and News

AN ANATOMICAL LANDMARK

IT might be thought that when a new book is described by a reviewer as "not wanted", "low", and "unscientific in tone", it could have little hope of success And when its publisher goes out of business and its young author dies soon after preparing a second edition, the work must surely disappear Yet Mr Henry Gray's *Anatomy*, which suffered this vile concatenation of events, has survived, and today it prospers increasingly, as Mr William Longman was able to relate at a dinner given in Stationers' Hall, London, on Sept 18 to celebrate the centenary of its first appearance Prof T B Johnston, who has seen "Gray" through nine editions since 1930, ruefully admitted that fifty-seven years ago, when he traded his "Liddell and Scott" for "Gray", he felt at first that he had made a bad bargain. Anyone buying the centenary edition, though he must dig deep in his pocket, is less likely to be seized with regret than with gratitude to Professor Johnston and his two associates, Professor D V Davies and Professor Francis Davies, for keeping their charge so free from the marks of age Textbooks may come and go, but "Gray", it seems, remains for ever, a welcome landmark in a shifting landscape

OLD PEOPLE WAITING FOR BEDS

IN 1951 the Hospital Personal Aid Service for the Elderly was set up by King Edward's Hospital Fund to visit in their homes old people who are awaiting admission to hospital The service visits only at the request of the hospital staff, and in their report for 1957 they say that during the year they visited 1765 old people on behalf of 15 hospital management committees On their visits the caseworkers of the service collect information about the patients' home circumstances, which is a useful guide to the hospital both in assessing priority for admission and later in arranging for discharge The visits also ensure that waiting-lists are kept up to date and that the names of patients who no longer want a bed are removed. The service is able to report that since it began its work in 1952 the percentage of patie[illegible] [illegible]ho have to wait over two months for a bed has fallen fro[illegible] 23 to 2, and that in 1957 66% of their patients were a[illegible]ted within a week. The address of the service is New Cr[illegible] General Hospital, Avonley Road, London, S.E.14

FACIAL ECZEMA IN NEW ZEALAND SHEEP

AN important advance in the knowledge of the ætiology of facial eczema has been reported by Dr C P McMeekan from the Government Animal Research Station at Ruakura, near Hamilton where the elusive toxic factor has been identified with the fungus *Stemphylium botryosum*

The disease (writes our New Zealand correspondent) affects mainly sheep, and is almost entirely limited to the North Island, though cattle are also affected and the guineapig can be used for laboratory studies Jaundice and sores on exposed parts of the body—especially around the face—are attributed to liver damage and the circulation of photosensitive breakdown products The liver lesion is essentially a cholangitis affecting the smaller ducts, and when severe can lead to obliteration and fibrosis

The dangerous time of year for outbreaks of facial eczema is autumn, when warm rains encourage the growth of fresh young grass—particularly in the ryegrass area As yet the only useful palliative measure has been to crowd sheep together to prevent their getting too much "toxic" grass, and warnings are issued each season when conditions are thought to be conducive.

Though many people—farmers as well as scientists—have incriminated a fungus or other live product as the causal agent, there has previously been no proof of such a theory For many years research has been predominately chemical and aimed at identifying a toxic substance in grass

The present success followed the observation by a farmhand that a fine cloud rose from his mower when he was cutting the "toxic" grass He found some mycelial growth at the roots of the grass, and later scraped a fine black deposit off the blades of the mower These both gave positive empirical "beaker" tests for toxicity, and cultures of the fungus have yielded an extract which reproduces facial eczema in guinea-pigs and lambs

Much remains to be done In particular it is not known why the fungus is widespread, although the disease is not But the team of four special chemists and pathologists from Great Britain who will reach New Zealand early next year to carry out further research will now have a much more promising task

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Royal Society of Tropical Medicine and Hygiene

The opening meeting of the session will be held at 26, Portland Place, London, W 1, on Thursday, Oct 16, at 7 30 P M, when Sir Philip Manson-Bahr will give the first Manson oration He will speak on the March of Tropical Medicine during the last Fifty Years

St Mary's Hospital, Manchester

On Friday, Oct 31, at 4 30 P M, at the Clinical Sciences Building, York Place, Manchester, 13, Prof A M Claye will give the Lloyd Roberts lecture His subject will be The Teaching of Obstetrics—New Edition

A New Teaching Hospital

The Minister of Health has announced that he has authorised the Board of Governors of the United Cardiff Hospitals to appoint architects for the new hospital and medical school to be built at Cardiff He understands that the board intends to hold an architectural competition

A City Sponsors Research

The Mayor of New York has announced (*New York Times*, Sept 18, 1958) the creation of the New York City Health Research Council with an initial income, from tax appropriation, of $600,000 The council is to sponsor public and private research, and priority is to be given to problems of ageing, childbirth and infant care, mental illness, accidents, *heart-diseases, environmental hazards, including air pollution* and radiation, and patient [illegible]

New Surgical Block at Guy's

On Sept 19 Lord Nuffield, president of Guy's Hospital, London, laid the foundation stone of its new surgical block

The 11-storey building will have 10 operating-theatres, 14 wards, and maternity, radiotherapy, and casualty departments In all it will have 378 beds It is hoped that it will be ready in 1960 The block will cost about £2¼ million

North Western Thoracic Society

This society will hold its first meeting of the session on Thursday, Oct 16, at 5 P M, in the Clinical Science Buildings, York Place, Manchester, when Dr Robert Coope will give a presidential address on Sundry and Manifold Changes

British Institute of Radiology

The annual congress and exhibition of this institute will be held on Thursday and Friday, Dec 4 and 5, at Church House, Westminster, London, S W 1 The subjects chosen for discussion include subarachnoid hæmorrhage, chronic bronchitis and emphysema, treatment of carcinoma by supervoltage radiation, and radioisotope techniques Further particulars may be had from the general secretary of the institute, 32, Welbeck Street, W 1

Parkes Weber Collection

Dr F Parkes Weber, who is now 95, has presented to the Wellcome Historical Medical Library the collection of manuscript notes, reprints, and case-reports of rare diseases which he has brought together in the course of his career as a physician and medical writer His books, *Rare Diseases and Some Debatable Subjects* (2nd ed, 1947) and *Further Rare Diseases* (1949), were based on a selection of this material A general index to the collection will be prepared by the Wellcome Library, where it may be consulted in due course (together with the original records and rep[illegible]

Dr. Robert Heilig Library
S. M. S. Medical College

International Association of Gerontology

The European clinical section of this society will hold first meeting in Sunderland from Oct 1 to 4 The subje chosen for discussion are genitourinary disturbances in age, ageing and arteriosclerosis with particular reference anticoagulant therapy, and confusional states in the elde Further particulars may be had from the hon secret Dr E Woodford-Williams, The General Hospital, Sunderla

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The annual dinner of the Glasgow University Graduates in Y shire will be held at Leeds University on Friday, Oct 17 Fur particulars may be had from Mr James Wishart, 33, Manor R Bradford, 1

The London Hospital old students' dinner will be held at Trocadero, Piccadilly, W 1, on Thursday, Oct 9, at 7 45 Tickets (37*s* 6*d*, or 27*s* 6*d* for those qualified less than five ye may be had from Dr R R Bomford, London Hospital, E 1

The annual students' dinner of Leeds School of Medicine wil held on Friday, Oct 31, at 7 30 P M, in the Griffin Hotel, I Lane, Leeds, when Dr F F Hellier will be in the chair

Semipermanent exhibitions will be held at the Institute of Der tology, Lisle Street, London, W C 2, during the winter The f from Oct 1 to 28, by Dr J P O'Brien, will be on the sweat-reten syndrome

The second number of the *Cerebral Palsy Bulletin* (summer, 1 contains the late Dr H C Cameron's last article, in which he cusses spasticity and the intellect As an example of a spastı brilliant intellect he cited Lord Byron, whose lameness Dr Came believed to be due, not to a club-foot, but to spastic paraplegia effectively supported this retrospective diagnosis by contempor descriptions of Byron's gait Copies of the Bulletin (2*s* 6*d*) may *had from the secretary of the society, 28, Fitzroy Square, Lond* W 1

From Monday, Oct 13, the address of the South West Me politan Regional Hospital Board will be 40, Eastbourne Terr London, W 2

CORRIGENDA *Chlorpropamide*—In last week's letter by Dr J Walker (p 641) we erroneously reproduced the start of the sec sentence of the second paragraph as "*43 diabetics had ch promazine* " This should have read "43 patients had ch propamide "

Accidental Hypothermia—In Dr Moylan's letter on this sub last week, a reference to Dr Emslie-Smith's case 7 was inadverte omitted and it should be made clear that Dr Moylan's compari was with this case only His remarks on the inclusion of endogen myxœdema hypothermia under the heading "accidental", simil referred to case 7 only

Appointments

CARRICK JESSIE D, M B St And assistant M O (maternity and child welfa
    Cleethorpes area of Lindsey
CONNOLLY, R C, F R C S surgeon, department of neurological surgery,
    Bartholomew's Hospital, London
COOPER, P R, B M Oxon, D P H, D T M, senior M O, London Airpor
CRAFT, M J, M D Lond, M R C P, D P M consultant psychiatrist to
    designated medical superintendent, Balderton Hospital, near New
EARL, C J M D Lond, M R C P physician National Hospital, Qu
    Square, London
GINEVER DOREEN M, M B Manc. assistant M O and school M O, Horsfo
    near Leeds
GOULD, W L P, L M S S A assistant M O, Monmouthshire refraction
MAIR, W G P M D Aberd pathologist, National Hospital Qu
    Square London
RAMSAY W W M B Belf, D Obst., D P H assistant M O H and sch
    M O Gloucestershire
RAPER, A B, M D, B Sc Leeds, M R C P, D T M & H pathologist Uni
    Bristol Hospitals
TOWNSEND, MARY, M B Lond, M R C P D C H assistant M O, Halifax
WHITFIELD, AUDREY P, M B Lond principal M O, London Airport

Colonial Appointments

BASSEY, E E, L S M Nigeria medical superintendent federal medi
    department Federation of Nigeria
FENDALL N R E M D B SC Lond, D T M & H A D M S, Kenya
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